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INTEGRATED STUDY MASTER'S THESIS

Medication-Related Osteonecrosis of the Jaw in Women with Breast Cancer. A Literature Review

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ABBREVIATIONS

AAOMS - American Association of Oral and Maxillofacial Surgeons

ARDs - Antiresorptive drugs

BMAs - Bone modifying agents

BPs - Bisphosphonates

BRONJ - Bisphosphonate-related osteonecrosis of the jaws

CTIBL - Cancer treatment-induced bone loss

DNB - Denosumab

MRONJ - Medication-related osteonecrosis of the jaw

OMFS - Oral and maxillofacial surgeons

ONJ - Osteonecrosis of the jaw

SREs - Skeletal-related events

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 (BPs) and Denosumab (DNB) are key bone-modifying agents (BMAs) used to target bone metabolism, reduce metastatic risk, and enhance adjuvant therapy efficacy in early-stage breast cancer. However, the usage of these agents carries risks, including adverse events such as osteonecrosis of the jaw (ONJ). Due to the impact of these drugs on the jaw bone, this condition is now known as Medication-related osteonecrosis of the jaw (MRONJ).This literature aims to provide a comprehensive investigation into MRONJ in the context of breast cancer treatment, with a specific focus on the effects of antiresorptive drugs (ARDs) such as BPs and DNB. Moreover, the study seeks to address the key question of how the use of ARDs impacts the occurrence of osteonecrosis of the jaw in women with breast cancer. The method of this study is to conduct a literature review to collect information on MRONJ in breast cancer patients. PubMed and Google Scholar databases were searched for English-language articles published between 2012 and January 2024. MRONJ 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 ARD. However, despite growing awareness of MRONJ within the medical community, doctors and dentists still have a poor understanding of the subject. Therefore, this research provides clear, practical guidelines to help prevent, manage, and treat MRONJ in breast cancer patients based on the best evidence review of currently available literature. In conclusion, dentists should follow particular protocols that are published in literature when treating patients who are in pretreatment or under high-dose antiresorptive therapy. The main goals of treating patients with MRONJ or at risk are to prevent and maintain quality of life. Therefore, dental students and dental specialists need to stay updated and pay attention to this side effect.

KEYWORDS: Breast cancer; Antiresorptive drugs; Bisphosphonate; Denosumab; Osteonecrosis of the jaw; Bone metastasis.

1 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 an important role in harboring 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). BPs and DNB 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 DNB 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 remodeling 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 it is crucial for dentists from different specialties and postgraduate and undergraduate dental students to 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 have a poor 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 on this topic (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, thereby improving patient outcomes and enhancing the overall quality of breast cancer care.

2 AIM

The aim of this study is to conduct a comprehensive investigation into medication-related osteonecrosis of the jaw (MRONJ) in the context of breast cancer treatment, with a specific focus on the effects of antiresorptive drugs (ARDs) such as bisphosphonate (BPs) and Denosumab (DNB).

3 OBJECTIVE

The purpose of conducting this literature review is to achieve the following objective:

- To review clinical manifestations of medication-related osteonecrosis of the jaw (MRONJ) in breast cancer women who have been prescribed antiresorptive drugs (ARDs).
- To evaluate the pathophysiology of medication-related osteonecrosis of the jaw (MRONJ) in this patient population group treated with antiresorptive drugs (ARDs).
- To determine the risk factors and incidence of medication-related osteonecrosis of the jaw (MRONJ) in breast cancer women treated with antiresorptive drugs (ARDs).
- To provide guidelines to the health care providers for managing and treating medication-related osteonecrosis of the jaw (MRONJ).

4 METHODOLOGY

4.1 SEARCH STRATEGY

The research will employ a literature review to gather existing knowledge on MRONJ in breast cancer patients. PubMed databases and Google Scholar were searched for English language articles published between 2012 and January 2024, for Case-Control, Case Review, Cohort Study, Systematic Review, and Literature Review. Lastly, 107 references were selected in this literature review.

4.2 SELECTIONAL CRITERIA

Inclusion criteria:

1-Patient Population:

Female patients diagnosed with breast cancer.

Patients currently undergoing or who have undergone treatment with antiresorptive drugs, e.g., BPs and DNB.

2-clinical diagnosis:

Patients with a confirmed diagnosis of MRONJ.

Patients who have been diagnosed with the ICD-10-CM code M87.1.

3-Timeframe:

Studies and clinical records not older than 2012 to ensure relevance to current medical practices.

4-clinical records:

Articles that reported the Incidence of and risk factors for medication-related osteonecrosis of the jaw in women with breast cancer woman, articles that reported the role of BPs and DNB in Breast Cancer Therapy, and articles that showed MRONJ.

Exclusion criteria:

1- Non-Breast Cancer Patients:

Articles that show drug therapy for osteoporosis in older adults.

Articles that show drug therapy for cancer patients.

2- Patients not receiving antiresorptive drugs.

Other drugs therapy for breast cancer.

3- Insufficient Clinical Data:

Clinical records lack essential information on patient demographics, cancer stage, antiresorptive drug details, or MRONJ diagnosis and management, and no full text is available.

4-Animal studies:

The mechanism of bisphosphonates on mature endothelial cells in vitro and vivo.

5 BREAST CANCER

5.1 DEFINITION

Breast cancer is a type of cancer that primarily affects women. It happens when cells in the breast begin to grow abnormally and out of control. Breast cancer usually originates in the milk ducts or lobules of the breast tissue. It encompasses various types, categorized based on the distinctive characteristics of the affected cells (1).

5.2 RISK FACTORS

Various studies have identified different factors that correlate with the risk of breast cancer development or progression. Some risk factors strongly associated with the disease include late age for marriage and first childbirth and late menopause age. Late age at marriage and childbirth can result in a lack of breast tissue differentiation, increased exposure to non-estrogenic mutagens, and genotoxicity by estrogen (11). Late menopause, which occurs after the age of 50, can result in prolonged exposure to estrogen for women (12); at the same time, there is also a connection between the female genital organs and the mammary glands, which means that low-grade cancers of the cervix, uterus, and other organs often cause breast cancer (13). One study estimated that women on non-vegetarian and high animal-fat diets have a higher chance of developing breast cancer than women on a vegetarian diet. Additionally, poor physical activity and obesity (high waist to hip) have also been correlated with a higher risk of breast cancer. Furthermore, a study found that moderate alcohol consumption of >35-44 grams/day increases the risk of breast cancer by 46% (11).

5.3 CLASSIFICATION

Breast cancer is a type of cancer that varies in its characteristics, making it essential to classify and diagnose accurately to determine treatment options. The classification aims to predict the tumor's behavior and diagnose the disease. The primary assessment of breast cancer involves evaluating two factors: first, the typing and grading of the tumor to determine its severity, based on its histologic subtypes and grade detailed in the WHO tumor classification, and second, the staging of the tumor, based on tumor size, nodal status, and distant metastasis (TNM staging) (14). Additionally, the routine assessment of breast cancer includes checking molecular behavior (15). Histological diagnosis of breast cancer is based on the evaluation of certain features, individually and in combination, including the cytological and architectural features of the proliferating cells, tumor-associated stroma, demonstration of the presence or absence of myoepithelial cells at the epithelial stroma interface (16).

There are more than 20 different histologic types of invasive breast cancers. However, the most prevalent type is infiltrating duct carcinomas, no particular type (IDC-NST), which accounts for

around 70% to 80% of all invasive cancers. The second most common type is invasive lobular carcinoma (ILC), which constitutes about 10% of invasive cancers. The rest are rare, including mucinous, cribriform, micropapillary, papillary, tubular, medullary, metaplastic, and apocrine carcinomas (17). Although IDC-NST has no specific morphologic characteristics of any other types, most breast cancers fall into this category. However, this classification cannot fully represent the biological diversity of breast cancers (15).

Based on molecular evidence, breast cancer can be divided into three groups: those expressing hormone receptors estrogen receptor (ER+) or progesterone receptor (PR+), those expressing the human epidermal receptor 2 (HER2+), and those that are triple-negative breast cancer (TNBC) (ER-, PR-, HER2-). Treatment approaches should be based on the molecular characteristics of breast cancer (18).

5.4 STAGES

Breast cancer is divided into several stages based on the tumor's size, whether it has spread to the lymph nodes, if it has metastasized, and the presence of specific biological markers. There are four stages of breast cancer. Stage 0 refers to non-invasive breast cancer. Stages I, IIa, and IIb are categories of early invasive cancer, and stages IIIa and IIIb are locally advanced breast cancer. All of these stages are non-metastatic. At the end stage IV, which indicates metastatic breast cancer, is the final stage, and the treatment for each stage is different (19).

5.5 DIAGNOSIS

To quickly and accurately screen breast cancer, many diagnostic methods based on imaging and molecular biotechnology have been developed. In some articles was mentioned that it is helpful to diagnose and treat patients with breast cancer by measuring the level of certain biomarkers, in another review, many diagnostic methods were described for different types of breast cancer patients, such as mammography (MG), ultrasonography (US), magnetic resonance imaging (MRI), nucleic acid hybridization system (NAHS), real-time fluorescence quantitative PCR system (RT-qPCR), protein hybridization system (PHS), flow cytometer (FCM) and so on which each method is valid for the specific type of breast cancer (20).

5.6 TREATMENT

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 subtype of cancer. Following systemic therapy, surgical interventions or radiation may be advised to mitigate the impact of tumor burden on the patient's quality of life (18,19).

Preoperative therapy: The purpose of preoperative systemic therapy is to reduce the size of breast tumors that can be removed through surgery. This treatment also allows for sentinel lymph node biopsy (SLN) instead of axillary lymph node dissection (ALND) in cases where axillary nodes cannot be detected. Preoperative therapy is generally not recommended for early invasive breast cancers (I, IIa, IIb) because tumors are often small enough to be removed through a lumpectomy. However, preoperative chemotherapy is used for patients with large primary tumors that are concerning breast size and wish to undergo breast-conserving surgery (18–20).

Postoperative therapy: Postoperative therapy often involves radiation treatment after surgical removal of breast cancer. The primary purpose of radiation therapy is to eliminate any remaining subclinical disease. It is typically recommended for patients who have undergone lumpectomy and for those with high-risk, node-positive disease who have received mastectomy (21). Approximately two-thirds of breast cancers are hormone receptor-positive and can be treated with endocrine therapies such as tamoxifen and aromatase inhibitors (19). Chemotherapy is another treatment method that involves the use of drugs to shrink the size of tumors before surgery (19).

Other therapy: For postmenopausal women who have undergone surgery for non-metastatic breast cancer and are receiving aromatase inhibitor therapy, it is recommended to also receive antiresorptive therapy. This additional treatment can help reduce the risk of developing bone metastases and fractures and improve survival rates. For patients with advanced breast cancer who have metastases to the bones, it is recommended to receive treatment with DNB or BPs such as zoledronic acid. These therapies have been proven to decrease the adverse effects of metastases on the bone, such as fractures and hypercalcemia (18,19).

5.6.1 TREATMENT IN EARLY-STAGE

It has been found that disseminated tumor cells can be identified in the bone marrow of around 25% of patients who have early-stage breast cancer. Moreover, the presence of these cells is linked with an adverse prognosis, as it increases the risk of recurrence (5). Recent studies have proposed the utilization of selective BMAs as adjuvant therapy, particularly for postmenopausal women with early-stage breast cancer (25). This recommendation stems from the association between low estrogen levels in this population and accelerated bone resorption (5). 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. However, adjuvant dosages are lower than those used for metastatic bone disease but higher than those used for osteoporosis or at the same dose (22). according to joint

guidelines from Cancer Care Ontario (CCO) and the American Society of Clinical Oncology (ASCO), adjuvant BPs therapy in postmenopausal women should involve zoledronic acid administered every six months for 3 to 5 years. A study conducted by Michael Gnant shows that in early-stage breast cancer, women who were treated with aromatase inhibitors and used DNB 60 mg every six months for three years experienced a significant improvement in bone health, reducing fractures by 50% (23). Another study by Robert Coleman suggests that DNB affects breast cancer outcomes rather than bone health (24). However, in patients with prevention and treatment CTIBL, DNB was shown to significantly delay the first clinical fracture and improve bone health compared to BPs (25). The study conducted by Mauceri suggests that breast cancer patients receiving low doses of bone BMAs for the prevention of CTIBL may have a similar risk of MRONJ as those with osteoporosis. Clinicians, particularly dentists, may not fully grasp the emerging risk of MRONJ in these patients, potentially leading to either overestimation or underestimation of MRONJ risks and preventive measures. Moreover, there is a risk of overlooking the need to enhance preventive protocols for MRONJ when transitioning to high doses of BMAs for treating bone metastases. Therefore, breast cancer patients on BMAs in the early stage should undergo regular MRONJ prevention monitoring, as they may switch to higher BMA doses in the future, increasing their MRONJ risk (8).

5.6.2 TREATMENT IN METASTASIS STAGE

Metastatic breast cancer can lead to metastatic disease in up to 80% of individuals, which can cause skeletal-related events (SREs). Patients with bone metastases often exhibit increased expression of the receptor activator of nuclear factor kappa-B ligand (RANKL), which can lead to bone resorption and destruction by stimulating osteoclast activity. This process contributes to the development of SREs, such as pathologic fractures, hypercalcemia, spinal cord compression, and pain. Therefore, bone-targeted treatments are necessary to manage these complications (26). Due to their significant impact on patients' quality of life and morbidity, it is crucial to minimize SREs. Adding BPs to the standard treatment of breast cancer patients with bone metastases is beneficial. Research has demonstrated that this addition can lead to a 15% reduction in the risk of SREs, a delay in the time it takes for SREs to occur, and an improvement in bone pain(27,28). Among all BPs, intravenous Zoledronic acid 4mg every 3-4 weeks is more potent and can be administered safely over 15 minutes (5). Subcutaneous DNB is a bone-modifying agent that inhibits osteoclast activity and reduces bone resorption, tumor-induced bone loss, and SREs by binding to human RANKL. It is dosed at 120 mg every four weeks and, in metastatic cancer, has been shown to delay the onset of SREs compared to zoledronic acid. The optimal treatment duration with these drugs remains controversial. The American Society of Clinical Oncology (ASCO) guidelines recommend that BPs and DNB should be given until there is a substantial decline in the patient's general performance status. The European Society for Medical

Oncology also suggests that these drugs should continue indefinitely under normal circumstances (26,29). International practice guidelines have not stated a preference for either DNB or BPs (30).

In the process of bone metastasis mechanism, cancer cells in bone need to undergo various adaptations to survive and thrive in their new microenvironment. This environment is highly vascularized and populated by various bone resident cells such as osteoblasts, osteocytes, osteoclasts, and other immune system cells in the bone marrow. The presence of a permissive soil known as the "pre-metastatic niche" in the bone microenvironment and the process of osteomimicry, the process for which "foreigner" cells mimic bone resident cells, are critical steps in the successful establishment of cancer cells in the bone tissue (31). These cells can escape the effect of adjuvant systemic therapy and subsequently proliferate to develop into metastatic disease (31).

The bone metastatic process is complex and has been the subject of several recent reviews. Originally known as the "vicious cycle," this schematic shows how cancers spread to the bone. The osteocyte is on the left side of the panel, and the breast cancer cell is on the right side(Figure 1).

1. A vicious cycle is created, where cancer cells and osteocytes (bone cells) stimulate each other's growth.

2. RANKL, a protein expressed by both osteocytes and cancer cells, attracts monocytes and promotes the formation of osteoclasts, cells that break down bone tissue.

3. Osteocytes release SOST (sclerostin) and DKK1, which inhibit the formation of osteoblasts (cells that build bone) and increase the expression of RANKL.

4. Activation of the notch signaling pathway promotes the death of osteocytes and the growth of cancer cells.

5. When osteocytes die, they signal for osteoclasts to break down more bone.

6. The enzyme complex CD39/CD73 hydrolyzes ATP (adenosine triphosphate) to adenosine, which binds to receptors on cancer cells to promote their growth and spread.

7. Adenosine also increases the activity of osteoclasts, leading to further breakdown of bone.

8. Finally, extracellular adenosine promotes Treg activity and immune tolerance.

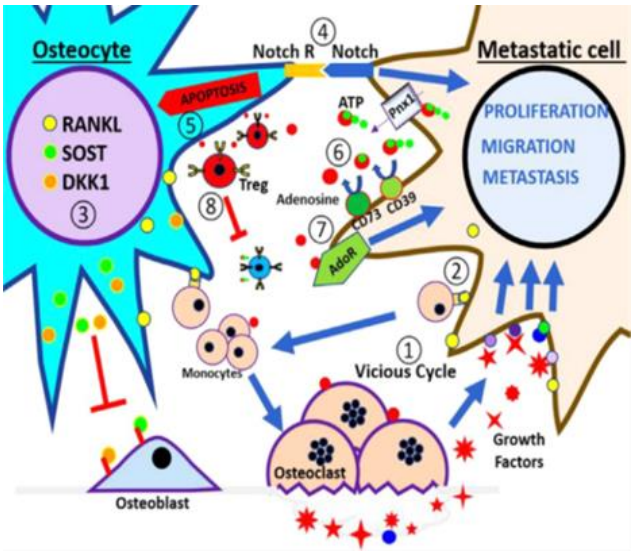

Figure 1. Schematic representation of when cancers go to bone. Adapted from (4)

5.7 IMPACT OF BREAST CANCER TREATMENT ON MRONJ

Breast cancer is the most commonly diagnosed cancer among women. It is estimated that in 2023, around 2.3 million new cases of breast cancer have been detected globally. Due to improvements in breast cancer diagnostics and treatment, the number of breast cancer survivors has grown significantly. As of 2020, there were approximately 7.8 million breast cancer survivors who had completed five years post-treatment. However, this number is expected to continue to increase, highlighting the need for better knowledge of the late effects of the disease and its treatments. One such possible late effect could be MRONJ (32). MRONJ is considered a potentially severe complication of BMAs in breast cancer patients (8). Noteworthy, it is important to remember that breast cancer patients may develop bone metastases during their clinical history (33), which can increase the risk of MRONJ due to the required high doses of BMAs. It is also worth noting that female breast cancer patients may have received low doses of BMAs in the early stage and also to prevent primary osteoporosis before starting cancer therapy. As a result, their cumulative dose of BPs or duration of BMAs intake will be increased (8).

6 ANTIRESORPTIVE DRUGS

ARDs are essential in preventing SERs and CTIBL in patients with early and metastatic stages of breast cancer. BPs and DNB are the most effective and commonly used ARDs in clinical practice. However, it is important to note that while more potent antiresorptive agents such as zoledronic acid and DNB offer greater efficacy, they also pose a higher risk of contributing to the development of MRONJ (34,35).

6.1 BISPHOSPHONATES

BPs are medications that can reduce bone loss in cancer-related conditions. They can be administered orally, such as alendronate and risedronate, or through injections, such as zoledronic acid and ibandronate. This study primarily focuses on zoledronic acid because it is more commonly associated with the development of MRONJ. According to the American Society of Clinical Oncology, the recommended dose of zoledronic acid is 4 mg every 3-4 weeks for bone metastases and every six months for early-stage disease (5,23,34,36).

6.1.1 MECHANISM OF ACTION

BPs are synthetic compounds similar to a natural substance found in bones called pyrophosphates. These synthetic compounds are designed to mimic the function of pyrophosphates in the bone matrix. There are two types of BPs: simple and nitrogen-containing. Nitrogen-containing BPs mainly affect bone density and have an adjuvant effect in cancer treatment (2). According to the pharmacokinetics theory, BPs not only leave the body through the kidneys but are also released in circulation and absorbed in bones while new bone is being formed. They are stuck in the bone until the bone breaks down again. This is why they have a long half-life (37). In the concept of the effect on bone density, simple BPs are broken down by osteoclasts, which are cells responsible for bone resorption, into methylene–containing analogs of adenosine triphosphate (ATP), which mess up osteoclast energy production and promote their apoptosis (2). Nitrogen-containing ones are even stronger for stopping bone resorption. They act by reduction of the isoprenoid lipid FPP and geranylgeranyl diphosphate in the osteoclast. This happens by inhibiting a key enzyme called farnesyl pyrophosphate (FPP) synthase, which is part of a pathway called the mevalonate pathway that is important for osteoclast function (2,38). In other words, it can impair osteoclast resorptive ability and cellular integrity, also triggering apoptosis and reducing bone resorption (38). In cancer patients, BPs may indirectly reduce the development and progression of bone metastases, as well as overall skeletal tumor load (2). In addition to their positive effect on bone density, a growing body of evidence indicates that BPs exert a range of direct and indirect anti-tumor effects in *vitro* and in *vivo* murine (2). Preclinical studies in breast cancer models point to various additional possible mechanisms by which BPs improve survival, such as inhibition of tumor cell proliferation and induction of tumor cell apoptosis, inhibition of tumor cell adhesive and invasion, antiangiogenesis, synergism with anti-neoplastic drugs, and enhancement of immune surveillance (2,37). In breast cancer patients, zoledronate alone has been found to increase the level of tumor cell apoptosis (39). When combined with other cancer treatments, it helps the body clear out cancer cells that have spread. Therefore, BPs have benefits beyond just improving bone health(40). Another possible explanation for the anti-tumor effects of BPs is their ability to inhibit tumor cell

adhesion and invasion. These processes are essential for cancer metastasis which happens via changes in fibronectin and actin expression in tumor cells due to BPs exposure (41). BPs may also have an anti-angiogenic effect, which means they can prevent the formation of new blood vessels. Studies have shown that zoledronate can effectively inhibit tumor angiogenesis, prevent the differentiation and recruitment of certain types of cells that support tumor growth, such as endothelial progenitor cells, and also inhibit myeloid cell differentiation into tumor-associated macrophages (2). In addition, for individuals with metastatic breast cancer, zoledronic acid can help reduce vascular endothelial growth factor (VEGF) and angiogenesis as well as fibroblast growth factor-2 (FGF-2) and matrix metalloproteinase-2 (MMP-2) in patients (9).

6.2 DENOSUMAB

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 (36). 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 (42,43). It has also shown direct or indirect anti-tumor effects in preclinical models and clinical applications (44).

6.2.1 MECHANISM OF ACTION

For a better understanding of the mechanism of action of DNB, it is important to clarify the role of RANKL. The discovery of RANKL helped connect bone and the immune system and became an important key in the rise of bone immunology (45). The RANKL/RANK (Receptor activator of NF-kB) signaling pathway plays a crucial role in osteoclast differentiation and function. RANKL is a trimeric transmembrane protein with two receptors: the membrane-binding receptor RANK and the soluble bait receptor osteoprotegerin (OPG) (46). RANKL is expressed in the bone matrix, osteoblast precursor cells, osteoblasts, and osteocyte (1A), and RANK is expressed on the membrane surface of osteoclasts and osteoclast precursors. When RANKL binds to RANK, it leads to the differentiation of osteoclast precursor cells into activated osteoclasts (2,3,4,5A) (44,47), which release enzymes involved in the degradation of collagens and other proteins, cavity formation, and a decrease in bone mass (6A) (47) OPG naturally inhibits the activation of RANK signaling by competitively binding to RANKL and preventing it from binding to its receptor RANK (1A) (28) DNB works similarly to OPG, by blocking RANKL to RANK which inhibits the development of osteoclasts from precursor cells(7B) and the function and survival of differentiated osteoclasts (8B) and (48)this leads to a reduction in the

release of protein-degrading enzymes, promotes the refilling of resorption cavities by osteoblasts (9B) (Figure 2) (47) DNB is usually administered subcutaneously at a dose of 60 mg, and the maximum serum concentration of DNB typically reaches around day 10, although this can vary between 2 and 28 days. Serum levels of DNB then decline gradually over three months, with a half-life of approximately 26 days, which can also vary between 6 to 52 days. Alternatively, it can be administered in a dose of 120 mg every four weeks, and steady-state concentrations are usually achieved around six months after initiating treatment (49). In addition, many preclinical studies are exploring the activation of RANK/RANKL that can simulate various intracellular signaling pathways crucial for tumor proliferation. However, further investigation is needed to confirm this issue (44).

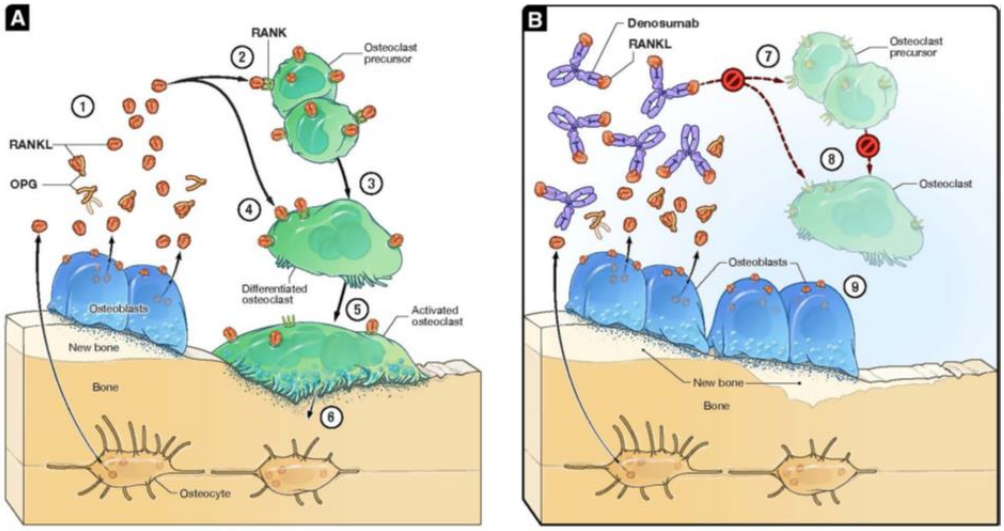

Figure 2. Denosumab mechanism of action. Adapted from (47)

7 DRUG EFFECTS

It is important to note that ARDs have both skeletal and non-skeletal effects. This study, however, focuses solely on skeletal events.

7.1 EFFICACY

BPs 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(38). 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 be beneficial for people with rare bone diseases like fibrous dysplasia, as well as bone cancer and bone metastasis (6). BMD responses to DNB follow a pattern similar to the BPs, although the increases are larger and continue through 10 years (38).

7.2 ADVERSE EVENTS

BPs treatment is generally well tolerated and the benefits of treatment almost always outweigh the side effects. However, it is essential to note that some side effects can occur, including hypocalcemia, renal toxicity, gastrointestinal symptoms, atypical bone fractures, and ONJ(2,5) ONJ was initially noticed in patients who had disseminated malignancy and were receiving monthly BPs infusions to prevent skeletal-related events (38). and is more commonly observed with higher dose density, prolonged duration of treatment, or shorter dosing intervals used in patients with metastatic disease (5). After the introduction of newer antiresorptive drugs such as DNB, distinct from BPs, this complication transitioned its nomenclature from BRONJ to MRONJ, indicating an area of bone exposure in the maxillofacial and intraoral region that exhibits signs of delayed or slow healing (7). However, it has been observed that patients with cancer who receive monthly DNB have a similar frequency as BPs. This suggests that its cause is related to low bone turnover rather than direct bone toxicity from BPs (38).

The risk of developing ONJ appears to be higher in oncology patients compared to those with osteoporosis. This heightened risk is likely due to the shorter dosing interval, as well as the effects of anti-neoplastic agents, such as angiogenesis inhibitors, immune suppression, and prednisolone treatment (6). Although the necrotic process may not be visible at first by the eye, the definition of ONJ is a clinical diagnosis based on the identification of an area of exposed bone in the oral cavity that remains unhealed for 6-8 weeks following appropriate management. It is usually triggered by an invasive dental procedure, such as an extraction (50).

7.3 POTENTIAL MECHANISMS FOR LOCALIZATION OF OSTEONECROSIS IN JAW

The reason ONJ is more commonly associated with the jawbone compared to other bones in the body is not entirely clear, but several factors may contribute to this phenomenon (51).

High bone remodeling rate: The jawbone has a high rate of bone turnover and is constantly undergoing remodeling. BPs and DNB work by inhibiting bone resorption, which can lead to impaired bone turnover. The jawbone's unique physiology, with its high turnover rate, may make it more susceptible to the effects of these medications (6).

Localizing factors: The jawbone may be more susceptible to localizing factors, including dental trauma, especially surgical extraction, infections, changes in oral bacteria biofilm profile, and impaired innate immune response specific to the oral cavity that can contribute to the development of ONJ (52–54).

Dental Trauma: The risk of MRONJ is highest when there is invasive dental trauma, such as tooth extraction or minor oral or periodontal surgery. Studies have shown that the incidence of MRONJ ranges from 51% to 82% in such cases (54,55). Furthermore, the risk of developing MRONJ is even higher when there is a local infection, abscesses, and poor oral hygiene (52,54,56).

Oral Mucosal Barrier: The oral mucosal barrier involves complex immune system components, and one study found that BP treatment led to increased oral bacterial load, accompanied by a significant decrease in antigen-presenting cells and decreased dendritic cell differentiation and activity, which can disrupt the local immune response(57). Therefore, bisphosphonate-related disruption of the innate oral immune system can lead to colonization of the mucosa with pathogenic bacteria and perpetuate necrosis following dental trauma (51).

Infections: Infection increases the acidity in the area of infection, leading to suppression of the mechanism of healing and thereby resulting in bone necrosis. This is because the jawbone is more susceptible to infections than other bones in the body (it is exposed to millions of bacteria in the oral cavity). In addition, lesions of MRONJ typically originate from the alveolar process and are often caused by infected root tips or periodontal pockets (14,51). Furthermore, when comparing anatomic sites most likely to be affected by bone necrosis due to medications, the mandible is more likely to develop osteonecrosis (73%) than the maxilla (22.5%). Since there is thin mucosa and a single blood supply for the mandible, it is more prone to necrosis and infections (58).

Oral bacteria: It is believed that the bacteria present in our mouth might play a role in protecting our alveolar bone against osteonecrosis. However, it is important to maintain a balance between managing infections and preserving the natural bacteria in our mouth, especially when prophylactic antibiotics are used during invasive dental procedures (31). Conversely, samples from MRONJ lesions have consistently shown microbial biofilm formation, and *Actinomycetes* were detected in 70% of those samples, and several studies have linked MRONJ to *Actinomyces* (88,89). It has been hypothesized that the mechanism of trauma-induced MRONJ simply includes creating access for pre-existing pathogenic bacteria(59), which is why MRONJ almost always starts at the alveolar process of the jawbone (51).

8 MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

8.1 DEFINITION

MRONJ 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).

8.2 DIAGNOSIS

MRONJ is a severe condition that can significantly affect a patient's quality of life and even lead to mortality. MRONJ can cause difficulty in swallowing, feeding, chewing, and speaking. Patients may also experience symptoms such as chronic sinusitis, swollen and painful mucous membranes, and other related issues (36).

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established specific criteria to diagnose MRONJ, which healthcare professionals commonly use. These criteria include (36):

- 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.
- Current or prior treatment with antiresorptive or antiangiogenic agents.
- No obvious metastatic disease or radiation history to the jaws.

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 (60). 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 (61).

8.2.1 CLINICAL PRESENTTATION

The primary clinical indicator of MRONJ is the exposure of bone, which can range from small exposed edges in an empty alveolus to the entire jaw or both jaws (62). Along with the exposed lesion, there are often signs of inflammation. Physicians must remain vigilant for MRONJ and are aware of the critical signs and symptoms such as increased volume of soft tissues and swelling, with or without suppuration, limited purulent inflammation or fistula, loosening of teeth, halitosis, cellulitis, non-healing sockets, and hypoesthesia or paraesthesia in the lower lip or chin region(42,63). The symptoms of osteonecrosis depend on the course of the disease and its spread to the surrounding structures (62). Pain is typically experienced in the acute stage, but after the onset of necrosis, it becomes asymptomatic. As the condition progresses, numbness, oroantral communication, and pathological fractures of the jaw can occur (36).

8.2.2 RADIOGRAPHIC FINDINGS

Radiological analysis is an important tool for monitoring the progression of osteonecrosis, assessing the extent of the disease, and detecting complications. The most common visible change is sclerosis, which thickens the lamina dura and narrows the periodontal ligament space. There may also be changes

in the trabecular pattern with mottled osteosclerotic changes or unexplained bone resorption, as well as persisting alveolar sockets after tooth extraction, can also be seen (62–64).

In patients where the bone is exposed, there may be more frequent occurrences of focal and diffuse bone sclerosing and formation of dead tissue, known as sequestration (65). In the late stages of separating necrotic bone, a distinct sequestrum with well-defined margins may be present (62).

MRONJ is usually diagnosed through a clinical examination. However, an orthopantomography (OPG) is necessary for an initial assessment of the extent of the disease. After an OPG, further investigation with computed tomography (CT) or cone beam computed tomography (CBCT) can provide a more detailed view of the lesion's progression. Magnetic resonance imaging (MRI) and scintigraphy may also be utilized, especially when surgical intervention is considered (42,62,63).

8.3 DIFFERENTIAL DIAGNOSIS

Dentists must be able to identify the signs and symptoms of MRONJ. Patients typically report pain and signs of infection as the most common symptoms, which can be easily confused with other diseases. Therefore, a differential diagnosis can be challenging but is also important (61). MRONJ must be distinguished from chronic sclerosing osteomyelitis, gingivitis, periodontitis, alveolar osteitis, sinusitis, odontalgia, atypical neuralgias, osteoradionecrosis of the jaw, and very rarely from oral Langerhans cell histiocytosis and idiopathic lingual mandibular sequestration (38,61). Moreover, it must be differentiated from squamous cell carcinoma (SCC); this can be extremely difficult in patients who are at risk for this type of cancer and have been treated with ARDs. Therefore, correct diagnosis requires thorough anatomopathological examination and clinical information (9,66).

8.4 STAGES

The AAOMS has proposed a comprehensive classification system for MRONJ based on the extent of clinical features. The classification system consists of four stages, each with its own distinct characteristics and management strategies. A group "at risk" is the initial stage and is described as including all those that have received antiresorptive medication and management strategies, including close multidisciplinary observation and good oral hygiene (9).

Stage 0: in this stage, patients may not show any clinical evidence of necrotic bone but may experience non-specific symptoms or clinical and radiographic findings. Some of these non-specific signs may include dull pain in the mandible, sinus pain, odontalgia without any visible cause, unexplained tooth mobility, fistula not associated with pulp necrosis or caries, and gingival swelling. Other symptoms may include resorption of alveolar bone that cannot be explained by chronic periodontitis, changes in

trabecular pattern, and alveolar or surrounding bone sclerosing. According to reports, up to 50% of patients with stage 0 disease have progressed to stage 1. Therefore, AAOMS suggests considering stage 0 disease as a potential precursor to MRONJ (36,62,63,67). The treatment for this stage involves a multidisciplinary approach and conservative, symptomatic care such as topical antibiotics, mouth rinses, and pain relief. It is also essential to refer the patient to an oral and maxillofacial surgeon (OMFS), who can perform a comprehensive oral examination and provide necessary dental treatment. In addition to these measures, follow-up visits are recommended every eight weeks to monitor the patient's progress and ensure that the treatment is effective. Patient education is also a crucial aspect of therapy at this stage. The patient must be adequately informed about the condition, the treatment plan, and the importance of maintaining good oral hygiene to prevent any further complications (9,62,63).

Stage 1: asymptomatic patients; at this stage, there are instances where the bone is exposed and necrotic, or there are fistulas that probe to the bone. However, despite these conditions, there is no indication of an ongoing infection or inflammation (67). For this particular stage, the treatment methods are similar to stage 0 but with some additional procedures. In addition to the standard treatment for stage 0, which includes oral hygiene instructions, symptomatic care, patient education, and periodic evaluation, additional interventions may be necessary. Specifically, if bone sequestrations are present, the bone may need to be removed. In this stage, if the patient does not respond to conservative therapy and sequestrectomy, then marginal resection and alveolectomy are recommended (9,36,68).

Stage 2: this stage encompasses patients who exhibit the presence of symptomatic necrotic bone visible during an examination. Additionally, patients with a fistula that probes to the bone, accompanied by pain, erythema, infection with or without purulent drainage, and complaints of painful symptoms, are also included. These symptoms are indicative of the progression of the disease and require immediate medical attention to prevent further complications (62,64,67). For the management of this stage , the main objective of therapy is to facilitate the healing process and prevent any future infections, and this is accomplished through a combination of treatment procedures mentioned previously, as well as antibiotic therapy and the use of chlorhexidine for antisepsis. Once the inflammation has subsided, the next step may involve debridement, which is the removal of dead or damaged tissue to promote healing (9,62). In more severe cases, segmental resection or partial maxillectomy may be necessary. Both of these procedures are aimed at removing any remaining infection and promoting the growth of healthy tissue. It is important to follow a comprehensive treatment plan during this stage to ensure the best possible outcome (36).

Stage 3: this state is quite severe and is characterized by exposed and necrotic bone, which can be accompanied by a fistula that probes the bone. The symptoms may include pain, erythema, and infection, and can also involve a pathologic fracture, extra-oral fistula, osteolysis that extends beyond the region of alveolar bone, for example, inferior border and ramus in 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 (36,67). For management at this stage, there are several treatment options available that can be considered. These options were explained in stage 2, and they include various therapies, procedures, and medications (9).

9 PATHOPHYSIOLOGY

The pathogenesis of MRONJ is not fully understood and is believed to have multiple causes. Many hypotheses have thus been proposed to explain the occurrence of the disease in that unique location (68). One of the proposed theories is the inhibition of bone remodeling or alternation of bone turnover of the jaw. This theory can explain this since one of the steps in bone remodeling is bone resorption by osteoclasts, which is requisite for osseous wound healing after invasive surgeries, including tooth extraction. Hence, the suppression of osteoclasts by ARDs could delay and impair osseous wound healing (69), and those drugs inhibit osteoclasts' differentiation and function, leading to their apoptosis (62). DNB, in particular, has been shown to reduce bone turnover compared to zoledronic acid (3). Another hypothesis suggests that MRONJ is caused by the inhibition of angiogenesis, which is the formation of new blood vessels. This phenomenon is supported by studies showing that MRONJ is typically characterized as avascular or aseptic necrosis. BPs, such as zoledronic acid, can directly inhibit angiogenesis in *vitro* and in *vivo* (70). and indirectly blocks blood vessel formation by targeting a type of immune cell called macrophages, which produce matrix metalloproteinase (MMP9) (71). Animal models have also demonstrated decreased vascularity in areas affected by MRONJ and reduced micro-vessel numbers during the early stages of bone healing (72). Furthermore, BPs inhibit angiogenesis, typically seen during the healing of extraction sockets. Both BPs and DMB have been shown to decrease arterial and venous areas and the overall vascularity of periodontal tissues during the early and late stages of MRONJ development (73). In the development of osteonecrosis, inflammation or infection plays a key role; invasive dental treatments like tooth extraction, root planning, and implant placement may cause bleeding and introduce oral bacteria into the bloodstream. Periodontal disease can also lead to bacteria entering the bloodstream temporarily, causing a reaction that triggers inflammation in the body. This bacteremia can disrupt the immune system, leading to systemic inflammation throughout the body. this scenario can be justified by decreasing the incidence of MRONJ in patients following improved dental hygiene. In this context, certain bacteria can produce lipopolysaccharides, which can increase the production of cytokines or directly regulate the production

of RANKL, which can lead to alterations in the bone matrix through the reprogramming of osteoclasts. These osteoclasts may then produce excessive proteins that break down bone. This disruption of normal bone maintenance triggers processes that acidify the bone environment, ultimately affecting bone turnover (71). Changes in pH levels caused by dental infections or invasive dental treatments may be the initial trigger for MRONJ. Additionally, when pH values are low, a process is triggered where BPs are released from the bone and activated to bind to osteoclasts and inhibit their activity, affecting osteoblasts, fibroblasts, macrophages, and lymphocytes (74). Studies on mice with induced rheumatoid arthritis showed more severe MRONJ, indicating a link between systemic inflammation and MRONJ severity (75). Patients with immune dysfunction such as rheumatoid arthritis, diabetes, or immunocompromised states are at significantly higher risk for MRONJ regardless of exposure to antiresorptive agents. This heightened risk extends to patients with metastatic or primary bone malignancies, as their compromised immune systems make them more susceptible to MRONJ, and 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. Studies have shown that altered numbers and patterns of regulatory T cells (Tregs) and inflammatory T-helper-producing interleukin 17 (Th17) cells may contribute to the development of MRONJ in mic (69). Several reports have identified single-nucleotide polymorphisms (SNPs) frequently found within regions of genes related to collagen formation, bone turnover, or metabolic bone diseases that can be associated with MRONJ. Sirtuin-1 (SIRT1) is one gene that promotes bone formation and regulates bone remodeling, and it is also involved in reducing inflammation. Upregulation of SIRT1 may have a protective effect against MRONJ. Other genes that have been implicated in increasing the risk of MRONJ are involved in angiogenesis, bone remodeling, and immune responses, including PPAR gamma, CYP2C8, and others. These findings indicate that MRONJ is a complex disease influenced by multiple genetic factors. However, current research suggests a weak or no association between measured genetic factors and MRONJ risk. To better understand the genetic predisposition to MRONJ, larger studies with diverse populations are needed (36).

10 RISK FACTORS AND INCIDENCE

MRONJ 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:

10.1 DRUG-RELATED RISK FACTORS

Drug risk factors depend on their specific pharmacokinetic and pharmacodynamic properties. The primary risk factor for MRONJ is exposure to DNB or BPs. However, it has been observed that MRONJ can arise following the use of other cancer therapies, such as inhibitors of angiogenesis, chemotherapy, hormonal therapy, cyclophosphamide, and corticosteroids, which can be associated with increased risk of MRONJ, and this can be explained by the fact that these medications can cause immunosuppression and thus, indirectly, affecting risk of local inflammation and consecutively the onset of MRONJ. The risk of developing MRONJ increases with more frequent administration or longer duration and subcutaneous or intravenous administration route at end higher dose per administration, which doses used in the metastatic setting versus in the osteoporosis or breast cancer in early stage setting and at the end breast cancer as an underlying disease was associated with an elevated MRONJ risk (10,62,68,76).

10.2 SYSTEMIC RISK FACTORS

Systemic risk factors refer to various conditions affecting 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 (50). Uncontrolled diabetes, for instance, can negatively affect bone tissue microarchitecture and healing through direct and indirect mechanisms, which can contribute to an unfavorable environment for MRONJ development. Smoking can also have a detrimental effect on the development and progression of periodontal disease. Although the exact pathogenic basis remains unclear, various hypotheses suggest alterations in the microbiota and impaired immune response may play a role. Therefore, patients undergoing MRONJ should be adequately informed and actively encouraged to quit smoking (77). Additionally, vascular diseases can cause impaired vascular systems, reducing blood circulation to bone structures, especially those with extensive blood supply, such as the lower jaw, which primarily comprises cortical bone. This diminished blood flow may potentially decrease the likelihood of MRONJ onset (76). It should be considered that genetics and age can also affect the risk of MRONJ (62,63). Moreover, some biomarkers can relate to MRONJ. The American Society of Bone Mineral Research Task Force has proposed a threshold for resorption marker, carboxy-terminal cross-linking telopeptide of type I collagen (CTX) levels (> 0.150 ng/mL) in patients receiving BPs, suggesting that invasive dental procedures may be safe if CTX levels are above this threshold. However, it is worth noting that low CTX levels (< 0.150 ng/mL) are common in patients undergoing antiresorptive therapy, which could pose a potential risk factor for invasive dental. Consequently, if this threshold is used, it may lack specificity. In the Cross-sectional study that Ana Laura Soares did, it was mentioned that

differences were observed in procollagen type 1 amino-terminal propeptide (P1NP) levels between oncological patients, despite similar concentrations of CTX between the groups in this study, P1NP was found to be increased in patients with bone metastasis, even with potent antiresorptive drugs. This suggests that P1NP may be a more effective marker for metastatic bone disease and MRONJ (10,42,50). 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.

10.3 LOCAL RISK FACTORS

It is important to consider any condition that can cause inflammation or infection in the dental supporting structures as a local risk factor. Specialists must promptly recognize and treat these factors to ensure the safe initiation of medical therapy (77). Here is a detailed overview of the local risk factors associated with MRONJ in breast cancer patients.

Anatomic Factors**:** certain anatomic features of the oral cavity may predispose individuals to MRONJ. These include bone exostoses, mandibular torus, palatal torus, and mylohyoid protrusion (78). These structures can contribute to mechanical trauma and compromise tissue health.

Subclinical Trauma: in some cases, MRONJ may happen spontaneously or without any identifiable initiating event; in these cases, subclinical trauma may contribute to bone necrosis in susceptible individuals (63), and it can also appear spontaneously in about 30% of cases (68).

Periodontal Disease and Apical Periodontitis: the elevated risk of MRONJ associated with periodontal disease, apical periodontitis, underscores the role of inflammation in its pathogenesis. This aligns with the theory that inflammation plays a central role in MRONJ development. Periodontal diseases perpetuate mucosal inflammation, providing a continuous stimulus that compromises mucosal integrity, and the periodontal apparatus facilitates the penetration of oral bacteria into the bone, initiating local inflammation processes. Moreover, the reduced activity of osteoclasts under ART significantly diminishes the body's defense mechanisms against bone infections. These observations support the hypothesis that local inflammations play a pivotal role in the pathogenesis of MRONJ (8,76).

Wearing Dentures: denture wearers, particularly those with ill-fitting or improperly maintained dentures, face an elevated risk of MRONJ. denture-associated sore spots also cause permanent mucosal inflammation and make micro lesions, which facilitate the penetration of bacteria into the bone and increase susceptibility to infection (76).

Tooth extractions: dentoalveolar operations are the most common identifiable predisposing factor for developing MRONJ. Several studies report that among patients with MRONJ, tooth extraction is cited as a predisposing event ranging from 62% to 82%(36). Also, the studies estimate the risk of MRONJ after tooth extraction is between 1.6 to 14.8 % in cancer patients exposed to IV BPs. There are two different theories about these risk factors. For the first theory, many studies have reported that tooth extraction is a major risk factor for the development of MRONJ in cancer patients receiving bone modifying agents' therapy, such as BPs and DNB, and thus, tooth extraction has been avoided. 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 associated with a 33-fold increase in the risk of MRONJ. Other similar studies have also reported that tooth extraction is a risk factor for developing MRONJ (79). However, in the second theory, some studies also reported that tooth extraction during bone modifying agents' therapy does not influence the risk of developing MRONJ. For instance, a non-randomized retrospective cohort study by Avishai found that tooth extraction may contribute to the development of MRONJ in nearly 20% of procedures. However, inflammation or infection is the most influential factor, with 95% of MRONJ cases being caused by it (80). Also, a retrospective observational study by Soutome et al. revealed that tooth extraction is not a risk factor for developing MRONJ in cancer patients receiving high-dose drugs but that preserving teeth that require tooth extraction is a risk factor for developing MRONJ. Therefore, if local inflammation/infection is treated before extraction, MRONJ may be avoided (79,80). In detail, while tooth extraction is considered a significant risk factor for MRONJ, it is typically recommended when the prognosis for the tooth is uncertain due to existing endodontic or periodontal diseases and conservative treatment options are not viable. In this situation, dental infections are the main reason for dental extraction. They are local risk factors already present for long periods before extraction. Indeed, among local risk factors, periodontal infections and the oral microbiome play crucial roles in the onset of MRONJ. These conditions trigger inflammatory responses that can directly or indirectly affect the alveolar bone, leading to bone resorption, and so under the effect of BMAs, the MROJ happens (8). Additionally, there is mounting evidence indicating that signs and symptoms of dental or periodontal infection are significantly associated with histological alveolar bone necrosis, even before dental extractions occur and MRONJ develops (81).

Dental implants: studies have shown that dental implants may increase the risk of MRONJ in patients treated with BPs or DNB due to two primary reasons. First, MRONJ appears to be related to peri-implantitis, which is an inflammation of the tissue around the implant that was placed before starting antiresorptive medication. It means that peri-implantitis can cause MRONJ, not just the presence of the implant. A retrospective single-center cohort study by Wickfond found that dental implants placed

before ART did not increase but instead decreased the risk of MRONJ onset. This could be due to the good oral hygiene conditions in patients caring for dental implants compared to those without dental implants. Second, MRONJ seems to be related to the insertion of implants in patients during or after taking antiresorptive medication. It is still unclear which of these two factors is more associated with the risk of MRONJ.

Moreover, the duration between implant insertion and MRONJ onset was significantly shorter in patients with cancer compared to those with osteoporosis. Specifically, the elapsed time was observed to be more than three times greater in individuals undergoing treatment for osteoporosis than in their counterparts receiving treatment for cancer. This highlights a potential variability in the manifestation of MRONJ based on the underlying medical condition. Therefore, it is essential to consider the specific context of the patient's health status (76,82).

Based on the works of literature, there are three main groups of patients who are commonly at risk of developing MRONJ (8,36):

1. The first group comprises cancer patients with bone metastases or myeloma who receive high doses of BMAs, often in conjunction with anticancer treatments such as endocrine therapy, antiangiogenics, and chemotherapy. They are at a high risk of developing MRONJ.
2. The second group includes cancer patients, such as breast cancer patients without bone metastases, who are at risk of non-metastatic bone fractures due to CTIBL. They receive BMAs to reduce CTIBL and improve prognosis. Their MRONJ risk is similar to that of patients with osteoporosis when receiving the same dosage of BMAs.
3. The third group consists of patients with osteoporosis or other non-malignant diseases who receive low-dose regimens of BMAs. They typically have the lowest risk of MRONJ unless their BMA treatment is prolonged.

10.4 MRONJ 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 (36). 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 the total population is 6.6%, while the incidence rate of MRONJ with zoledronic acid is 4.1% (3). This 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 reason why the incidence rate in the total population is higher than in the BPs population is due to the risk of MRONJ by constipation DNB, which is three times higher than that of zoledronic acid. In patients on DNB, MRONJ had developed

after 28 months, but in patients on zoledronic acid, the mean time to MRONJ was 41 months, and the incidence of MRONJ with DNB was 13.6%. Plausible explanations for the higher incidence and earlier onset of MRONJ in patients treated with DNB may be the different mechanisms of the medications and their effects on patients. For example**,** DNB can cause reduced bone turnover and delayed SREs compared with zoledronic acid (3). Allan Lipton's study comparing DNB with zoledronic acid in several cancer types demonstrated that bone turnover markers were significantly lower, and hypocalcemia was more common in the DNB group, which may suggest stronger bone affinity (83). Although MRONJ is a serious complication of antiresorptive treatment, the benefits of these medications, such as reduction of SRE and a better quality of life, predominate. Furthermore, if MRONJ develops, most patients can be treated surgically with sequestrectomy, block, or segmental resection, with complete healing achieved in the majority of cases (3). In recent randomized controlled trials on breast cancer patients without bone metastasis under a low dose of BMAs for CTIBL prevention, the incidence of MRONJ was observed between 0% and 0.5 (83,84). In the end, MRONJ continues to pose a notable risk for individuals undergoing treatment with ARDs for cancer-related bone issues. However, the chances of developing MRONJ can be reduced by conducting regular dental assessments and promptly addressing any dental issues (85).

11 DRUG HOLIDAY

A drug holiday is a temporary cessation of drug administration for any invasive procedure to reduce the risk of bone necrosis. Taking a drug holiday before dentoalveolar surgery remains a controversial issue (69), as some studies suggest it decreases the risk of MRONJ, while others do not show any significant difference in MRONJ outcomes(86). The rarity of MRONJ in these patient populations makes it difficult to establish or refute the efficacy of drug holidays (36).

Research shows that the effects of BPs and DNB drug holidays may be very different due to the different pharmacokinetic properties of the two agents(87). Phosphonate groups act as hooks and can accumulate bisphosphonate molecules in the bone matrix. Hydroxyl groups in drugs, such as Zoledronate, increase their binding affinity and potency (51). Research shows that matrix-bound bisphosphonate molecules concentrate in specific bone sites such as jaw bone for many years, and these drugs have a long half-life, which means that taking a break from them may not be effective in eliminating their effects. Even if a drug holiday is initiated to reduce the systemic effects of BPs, it is unlikely to affect the activity of the locally deposited bisphosphonate molecules (51,88).

It is important to note that DNB has a shorter half-life of 28 days and does not accumulate in bone tissue like BPs. Based on the pharmacokinetic properties of the drugs, it is assumed that patients who have received DNB may respond better to a drug holiday compared to those who have received

zoledronic acid (63,89). However, in most oncology patients, DNB is a life-prolonging medication that cannot be discontinued for a certain period. Others have concluded that a drug holiday does not affect the healing outcome in patients with MRONJ (90,91). Due to an increased risk of SREs during drug holidays, it is recommended that the decision to suspend antiresorptive therapy should be discussed among a multi-professional team on a case-by-case basis. The team should consider the potential deleterious effects of discontinuing the therapy, as the risks may outweigh the benefits. It is worth noting that this is still an area of active investigation (3,92).

12 PREVENTION STRATEGY

To prevent MRONJ, it is important to evaluate a patient's MRONJ risk group, along with any additional risk factors that may be present, and then create an individualized treatment plan (63). 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 that 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. Additionally, the development and implementation of educational programs become imperative to enhance interdisciplinary collaboration and deepen understanding among healthcare professionals regarding the benefits and potential side effects of bone-modifying agents across both dental and medical specialties (36,63,64,87,92).

12.1 ROLE OF DENTIST

The dentist plays a crucial role in patient care by assessing modifiable risk factors, establishing follow-up protocols, and maintaining open communication with oncologists. During initial discussions with oncologists, dentists must address key points such as the timing of BPs or DNB initiation to prophylactic dental assessments. This entails determining whether dental procedures should be conducted before commencing antiresorptive therapy or if immediate treatment is necessary, considering the patient's prognosis, overall health status, and other medications with potential oral side effects (92,93). Additionally, the dentist must conduct regular dental check-ups every six months (for metastatic breast cancer patients, receiving high-dose therapy every four months is recommended) (8), educate the patient about the importance of daily oral care, and encourage them to address any risk factors. This includes completing a comprehensive dental examination and providing both

conservative and non-conservative dental and periodontal interventions as necessary. Dentists need to continue motivating patients to attend follow-up visits and maintain excellent oral hygiene practices throughout the treatment phase. Additionally, dentists must regularly assess the patient's oral status and monitor changes in lesion status, promptly reporting any findings to the oncologist (93).

12.2 ROLE OF PATIENT AND PRIMARY CARE

It is important to be aware of the potential link between medications and oral symptoms, such as jaw pain, swelling or numbness, and non-healing sockets, and to report any such symptoms proactively. In addition, maintaining good oral hygiene practices, such as regular brushing, fluoride toothpaste, and mouthwash, can help prevent oral issues. It is also recommended that regular dental check-ups are attended to ensure any potential issues are caught early and properly addressed. In addition, a physician must also balance the risk of MRONJ with the benefits of BPs or DNB in reducing the risk of SREs (63,64,87).

12.3 ROLE OF DENTAL SPECIALIST (OMFS)

When consulting a dentist or oncologist about a patient with suspected MRONJ, it is recommended to refer them to a dental specialist for additional treatment management (65). The dental specialist will then assess symptoms, clinical stage, severity of the disease, functional impact, and overall prognosis based on clinical manifestations following an 8-week follow-up plan. Additionally, they should create a treatment plan based on stages, and all information should be shared with the oncologist. The disease outcome will be evaluated, and follow-up visits should occur every eight weeks (93).

12.4 ROLE OF ONCOLOGIST

It is highly recommended that oncologists make their patients aware of the significance of oral care before beginning any treatment. Therefore, they should encourage and refer their patients to undergo a thorough dental examination by a dentist to minimize any possible risks, and for patients recently diagnosed with MRONJ, oncologists should determine the duration and continuation or discontinuation of antiresorptive therapy according to the patient's situation and treatment plan. Furthermore, it is necessary that they provide the dentist with the patient's medical diagnosis and antiresorptive profile (63,93).

The management of MRONJ should focus on patient care and involve a collaborative network of healthcare professionals to ensure effective treatment, and the team needs to share resources and communicate regularly to develop an appropriate follow-up plan (50,63).

12.5 ROLE OF ONCOLOGY NURSE

Healthcare providers should remain vigilant regarding the association between bisphosphonates and dental health, ensuring effective communication with patients or caregivers to promote awareness and adherence to dental care recommendations. It is essential to ensure patients have access to dental care and advice, support oncologists in addressing oral symptoms, and facilitate seamless communication between oncologists and dentists for comprehensive patient care (63).

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

In the context of preventing MRONJ, it is essential to note that a standardized protocol has yet to be established. The literature presents a diverse array of protocols, spanning from antibiotic regimens to autologous platelet concentrates and even innovative approaches such as laser therapy (94). This underscores the need for further research and consensus in this area. The goal of the prevention of MRONJ is to eliminate dental risk factors and maintain a healthy oral environment (88). Patients are divided into two groups based on their history with ARDs. The first group, called the pre-treatment 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, referred to as the in-treatment phase, comprises patients who have already been exposed to ARDs. These patients will participate in an oral health assessment program to minimize local risk factors for MRONJ (95). To gain a better understanding of this topic, we will now discuss dental procedures in both the pre-treatment and in-treatment phases.

12.6.1 CANCER PATIENTS IN THE PRE-TREATMENT PHASE

As previously mentioned, the prevention of MRONJ involves a multidisciplinary approach. One of these disciplines involves the active participation of the patient. When patients with metastases cancer are being considered for treatment with DNB or BPs, the risk of developing MRONJ must be clearly explained by healthcare professionals in the context of maintaining skeletal health (63). It is crucial to educate patients about the importance of oral hygiene, including the use of fluoride toothpaste and mouthwash. Additionally, avoiding smoking and alcohol and scheduling periodic dental check-ups are highly recommended also inform them about the consequences of abstaining from preventive dental treatment. Providers should explain to patients the signs of MRONJ to monitor, including exposed bone, jaw pain, loose teeth, pus discharge, bad taste, non-healing sockets and sores, numbness, swelling, and erythematous gingival (64,87,96).

12.6.2 DENTAL TREATMENTS IN THE PRE-TREATMENT PHASE

In the pre-treatment phase, non-restorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery also should be completed. Preoperative and postoperative antibiotics, as well as antimicrobial mouth rinses, should be utilized (36). In cancer patients with poor or hopeless teeth or any other dental infection, if systemic conditions permit, initial antiresorptive therapy should be delayed after healing tissue due to invasive dental treatments such as dentoalveolar surgeries, and this means that before starting antiresorptive medications, there should be a waiting period of at least 45-60 days, allowing for the soft tissue to heal (36,95). In another study, Singh concluded that when a pre-treatment extraction is completed, the tooth should be removed atraumatically, and osseous healing should be complete, usually requiring 4 to 6 weeks before antiresorptive medication is started. This study emphasizes the importance of trying to avoid tooth extractions in patients who are undergoing high-dose drug therapy for cancer (87). Additionally, it is essential to note that other invasive procedures, such as implant surgery, preimplant bone surgery, and mucogingival surgery, are contraindicated during this phase. These procedures are not aimed at the elimination of infection and often have a rehabilitation/aesthetic aim. Moreover, they may carry an undefined long-term risk of developing MRONJ after the administration of ONJ-related drugs (97). However, for all other non-invasive dental procedures such as restorative dentistry, endodontic treatment, orthodontic treatment, oral hygiene, and non-surgical treatments and prostheses, which outcome is reliable, it is not required for delay for antiresorptive therapy. Suppose antiresorptive therapy cannot be postponed, and the patient requires invasive and necessary dental procedures. In that case, it is necessary to treat the patient in the treatment phase, not in the pre-treatment phase. These decisions must be made in conjunction with the treating physician, dentist, and other specialists involved in the care of the patient (36,95).

Medical oncologists play a vital role in educating their patients about the significance of maintaining optimal dental health and the effectiveness of prophylactic dental interventions in preventing MRONJ. Also, if a patient is undergoing chemotherapy, oncologists should briefly look for exposed bone when assessing for chemotherapy-induced oral mucositis. Dentists must perform an oral examination, including a radiographic assessment, and obtain a detailed dental history from patients before initiating antiresorptive therapy for malignant diseases (36,63). In this phase, it is important to identify local dental infections, especially those that involve the bone, such as marginal and apical periodontitis (63). Therefore, endodontic, dental prophylaxis, caries, restorative, and non-surgical periodontal treatment (If non-surgical methods fail to treat infections, periodontal and endodontic surgeries may be necessary.) should be completed as they are indicated to stabilize the oral cavity and remove potential sources of infection (64,87). Additionally, it has been observed that MRONJ can be caused by poorly

performed root canal therapy. Therefore, evaluating the tooth and performing pulpal testing is important to obtain a proper diagnosis and rule out MRONJ. The clinician's skill level in performing RCT should also be considered, as over- or under-filled canals can lead to MRONJ (88). Other considerations might include the general status of a patient's dentition and, if there are dentures, whether these are ill-fitting and for how long they have been worn (63). Individuals with full or partial dentures should have their mouths checked for any signs of irritation or injury of mucosal trauma, especially along the posterior lingual flange region, due to wearing dentures that are not fitting (36). and lesions within the mucosa, such as sore spots, provide a route for bacteria to reach the bone, causing inflammation (87). It is essential to integrate these assessments and interventions seamlessly into the patient's overall treatment plan, ensuring comprehensive care and minimizing the risk of MRONJ onset.

12.6.3 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 (95). Dental extractions or dental 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 (64). 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 (95). Spontaneous development of MRONJ without any invasive dental treatment has also been reported (64).

12.6.4 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. This regimen is initiated seven days before the planned dental procedure (96). Following the procedure, postoperative medical therapy includes a topical approach, which involves using a CHX mouthwash thrice daily for 15 days. Additionally, patients are recommended to undergo growth-promoting treatment, which consists of applying a gel containing hyaluronic acid thrice daily for the following 15 days (97,98).

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 (97).

Surgical Procedure Guidelines: During the surgical extraction, specific recommendations include the use of local anesthesia 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 (97). 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 important to have periodic clinical check-ups scheduled accurately at 3, 6, and 12 months (95). If the extraction socket has not healed after eight weeks, MRONJ should be suspected (64). Recent advancements in surgical techniques have introduced the use of autologous platelet concentrates (APCs) and /or 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 epithelization, particularly in patients undergoing bisphosphonate therapy (99). PRP, being 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 (99). The evidence suggests that PRF may intervene with bisphosphonate-induced effects on osteoclasts and mucosal cells, and also because the high level of leukocyte content serves to combat emerging infections in sites with challenging healing processes and it emerges as a favorable material in oral surgery, Plasma Rich in Growth Factor (PRGF) is another APCs, which contains various growth factors and shows the potential to induce mitosis of target cells, leading to favorable outcomes (94). Clinical observations reveal that adjunctive therapy with leukocyte–PRF (L-PRF) during tooth extraction in oncologic patients reduces MRONJ incidence (100). For those reasons, it should be considered a dentist-friendly material in oral surgery in all cases 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 (94). The combination of L-PRF and laser in patients cured with BPs showed physiological wound healing after a relatively short period of one month, and none of them experienced MRONJ (100).

When dealing with inflammatory-infective issues that can be resolved through endodontic or periodontal surgical procedures, the clinician must adhere to consistent guidelines, and this includes applying the same protocols that are relevant to dental extractions. The guidelines should cover critical aspects such as medical prophylaxis and surgical procedure guidelines (98).

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 (98,101). 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 vasoconstricting anesthetic 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 (101).

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 with caution to ensure regular removal of plaque. It is also important to periodically screen patients undergoing treatment to monitor their oral and periodontal health (102). 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 (8,102). 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. It is also important to educate individuals on proper home oral hygiene practices, which should cover both the oral cavity and dentures. These measures can help reduce the risk of periodontal infection (102).

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 (36,95).

Dental prostheses: It is recommended that cancer patients who use removable dental prostheses have a check-up every four months. During these check-ups, the goal is to constantly evaluate the fit of the dentures to ensure there is no compression or pressure ulcer, and it is crucial to minimize pressure on the oral mucosa and enhance stability (103). Additionally, it is advised that patients refrain from wearing their dentures for approximately 8–12 hours per day, especially during the night. When it comes to fixed prostheses, such as dental crowns or bridges, it is crucial to consider the biological width and avoid encroaching on the junctional epithelium. Ideally, supragingival prosthetic margins should be established to minimize trauma to the surrounding soft tissues and promote periodontal health (95).

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 (95).

13 TREATMENT

13.1 TREATMENT GOALS

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 prioritize and support continued oncologic treatment for those receiving antiresorptive therapy to control bone pain and reduce the incidence of SREs (36). The therapy of MRONJ depends on stages or, in other words, the degree of development of the disease, and it can be broadly classified into two main approaches: conservative (non-operative) and surgical (9,62), and decisions regarding surgical versus non-operative treatment should be personalized to each patient and adapted to their unique requirements. Evaluating the risk-to-benefit ratio is crucial in this process (104).

13.2 CONSERVATIVE TREATMENT

The effectiveness of conservative therapies in managing MRONJ is discussed in many literatures, and 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 potentially contribute to its development. Therefore, non-operative is mainly recommended, particularly in the early stage of MRONJ, but according to the AAOMS classification update 2022, it can be useful in all stages (36,105). conservative therapy includes systemic antibiotic therapy in combination with antimicrobial therapy and oral hygiene and sometimes removal of movable bony sequestrum segments and the extraction of symptomatic teeth from the exposed necrotic bone, and the main goal of those treatments is stabilization of lesions (77,105).

Antibiotic therapy: oral antibiotics are crucial for treating MRONJ infections. MRONJ infections are caused by a variety of microorganisms, including *Actinobacteria*, *Bacteroides, Firmicutes,* and *Fusobacteria*. Therefore, broad-spectrum antibiotics are recommended. In cases where oral antibiotics are not effective due to the presence of microorganisms that are resistant to them, intravenous antibiotics may be given for up to 6 weeks (9). Societies such as the AAOMS, the Italian Society of Maxillofacial Surgery (SICMF), and the Italian Society of Pathology and Oral Medicine (SIPMO) advocate for minimally invasive treatments, utilizing systemic broad-spectrum antibiotics and topical

antiseptics as the primary approach. However, the optimal antibiotic regimen for MRONJ treatment remains undefined (106). Ciobanu recommended conducting an antibiogram whenever feasible to guide antibiotic selection. For non-allergic patients, beta-lactams like Amoxicillin or Amoxicillin-clavulanic acid are considered suitable. Clindamycin is suggested for allergic individuals, although resistance from *Staphylococcus aureu*s and *Pseudomonas mendocina* may occur, necessitating alternative antibiotics such as Ceftazidime, Ceftriaxone, or Ciprofloxacin (106). Despite the lack of robust evidence, the literature suggests a treatment protocol involving antibiotic combinations such as Penicillin and Metronidazole as the first choice. This therapy typically lasts from 7 to 14 days at full dose, administered orally. Alternative antibiotics like Erythromycin, Clindamycin, or Ciprofloxacin may be used for patients allergic to Penicillin or Cephalosporin (105).

Antiseptic therapy: the use of chlorhexidine mouthwashes (e.g., 0.12% non-alcoholic solution and 0.2% alcoholic solution) is widely recommended for disinfection of the oral cavity in the presence of oral mucosal lesions (50). It suggests temporary use of 0.2% alcohol chlorhexidine during flare-ups of over-infection or in the perioperative period following oral cavity surgery. Additionally, for individuals with MRONJ who cannot undergo curative treatments due to certain health conditions or therapies, a maintenance protocol involving non-alcoholic chlorhexidine 0.12% is recommended. This maintenance protocol typically involves rinsing twice a day for one week per month (62). Although AAOMS treatment guidelines include oral lavage with chlorhexidine, it has been reported in other studies that this method does not effectively remove biofilm from exposed bone. Therefore, it is recommended to use a cotton swab or small toothbrush dipped in chlorhexidine to remove all plaque and debris from the exposed bone. This process is referred to as local wound care (61).

Pain relief therapy: patients with MRONJ often experience pain, which can indicate a more advanced stage of the disease. When chronic neuropathic pain is being treated with NSAIDs, opioids, ketamine, neuroleptics, or other drugs, it should be managed by specialists in analgesic therapy to avoid potential intoxication or reduced efficacy over time (105).

13.3 SURGERY TREATMENT

It is important to note that quality of life in oncological patients is a multifactorial issue with inherent sources of bias and confounding factors. In the past, guidelines for managing MRONJ discouraged surgical intervention due to inconsistent evidence of positive 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 (63). Even in earlier stages of MRONJ, where necrotic bone creates a nutrient base for microorganisms to colonize and further progress the disease, surgery can be effective. As a result, both

the American and Italian boards advocate evaluating the cost-benefit ratio on a patient-specific basis without restricting considerations based on the MRONJ stages (62,77). Decisions should be made individually for each patient, considering the goals of therapy, the patient's cancer prognosis, and any barriers to surgery to avoid over or under-treatment, and the type of procedures is determined according to the clinical staging of the disease. However, avoiding surgery for all patients who have advanced metastatic cancer has become outdated (63). Additionally, the necrotic bone removed during surgery is recommended to be sent for histopathological processing, as it may uncover metastases in the jaw specimen. However, this occurs in only a minority of cases. (36,62).

In the context of local surgical procedures for MRONJ, debridement and sequestrectomy are commonly considered. However, according to Davide De Cicco's study, those procedures should not be considered surgical interventions, but rather conservative therapies and surgical interventions are primarily categorized based on the extent of necrotic bone resection (77). However, other studies categorize those procedures as surgical interventions (9,62,68,105,107). Debridement is the surgical removal of necrotic bone tissue until a bleeding bone surface is found, and this procedure is performed when a viable bone is attached to the necrotic bone. On the other hand, sequestrectomy_removes necrotic bone sequestration, a portion gradually separated from the adjacent healthy bone in some cases, and both operations can be performed under local anesthesia (105,107).

Regarding extensive surgical procedures, AAOMS recommends segmental and marginal resection for the mandible and partial maxillectomy and alveolectomy for the maxilla (36). Segmental resection refers to the full-thickness removal of a skeletal segment, which interrupts its anatomical continuity, but marginal resection surgery involves removing only the affected tissue without disrupting the anatomical continuity of the bone (105). Therefore, the excision of vital margins should be carefully considered, especially in the initial stages, as it is associated with a higher success rate. The procedures will be performed under general anesthesia. It is recommended that antibiotics be prescribed before and after the surgery. The commonly prescribed antibiotic classes are Amoxicillin-clavulanic acid and extended-spectrum penicillin. Usually, patients will receive multiple courses of therapy, and the average duration of antibiotic administration is 28 days (77). For optimal healing outcomes in MRONJ, it is generally advised to perform a complete removal of necrotic bone, carefully smooth any sharp bony edges, and ensure thorough wound closure. Additionally, perioperative antibiotic treatment should be administered to help prevent infection and promote proper healing (36,63,105).

Additional possible therapy: there are several additional possible treatments for MRONJ. These include ozone therapy, laser therapy, the use of growth factors combined with antibiotics to reduce the lesion and relieve symptoms, and hyperbaric oxygenation. However, hyperbaric oxygenation is not

recommended for patients with malignant diseases because it can increase circulation and encourage the spread of disease. According to research, taking vitamin D supplements may be a low-risk and low-cost way to prevent or treat MRONJ in patients with vitamin D deficiency (62).

14 ENHANCING ANNOTATION SHEET RECOMMENDATIONS

In full prescribing information about BPs and DNB, which is written in the annotation sheet by the American Food and Drug Administration, 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" (43).

Using words such as "should" in the annotation sheet of DNB and BPs related to the treatment of breast cancer are non-committal words, and they are not appropriate so according to clinical guidelines in the pre-treatment phase expressed by Sven Ottoa (63) and Nita Singh (87) strongly recommend that it is essential for physicians to carry out an oral examination and take a brief dental history and it is most important educate patient about risk MRONJ and discuss the important of oral hygiene and dental treatments. The word "essential "indicates 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 dental examination and oral hygiene are crucial and obligatory in reducing the risk of MRONJ, and it is recommended to use stronger words such as "must" or "obligation" to emphasize the importance of this preventive measure in minimizing adverse effects that may occur due to these medications.

CONCLUSION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious disease that can occur in women with breast cancer, whether in both the metastasis or early stages. Clinical manifestations are based on clinical and radiograph findings, which will be categorized into four stages: during stage 0 of Medication-related osteonecrosis of the jaw (MRONJ), patients may not show clear evidence of bone necrosis but may experience non-specific symptoms, and in Stage 1 bone exposure and fistulas may be present without any signs of infection and patients are asymptomatic, Stage 2 includes patients with visible symptomatic necrotic bone or with a fistula that probes to the bone with the sign of infection, and at end stage 3 which this severe stage involves exposed and necrotic bone, with

accompanying various symptoms including pathologic fracture. The pathophysiology of Medication-related osteonecrosis of the jaw (MRONJ) is not fully clear; however, it is believed inhibition of bone remodeling, inhibition of angiogenesis, inflammation or infection, immune dysfunction, and genetic predisposition are predisposing factors. Systemic and local risk factors, such as invasive and some non-invasive dental treatments, anatomic factors, and periodontal disease, along with drug-related risk factors, all contribute to the development and severity of this disease. Therefore, understanding these factors is crucial for effective prevention and management strategies. The incidence of Medication-related osteonecrosis of the jaw (MRONJ) in breast cancer patients varies depending on the type of antiresorptive medication used. Studies have reported higher incidence rates with drugs like Denosumab (DNB) compared to Zoledronic acid. However, Medication-related osteonecrosis of the jaw (MRONJ) is a serious condition that is not yet fully understood. Therefore, postgraduate and undergraduate dental students and specialists need to have a solid understanding of Medication-related osteonecrosis of the jaw (MRONJ), stay up-to-date on the latest research, and pay close attention to this side effect not only for metastatic but also for early-stage breast cancer. Guidelines for the management and treatment of Medication-related osteonecrosis of the jaw (MRONJ) have been provided to professionals to ensure proper care for cancer patients.

GUIDELINES FOR DENTISTS

These instructions provide a comprehensive guide for dentists on managing cancer patients in both the pre-treatment and in-treatment phases to minimize the risk of developing MRONJ and ensure optimal oral health outcomes.

<table>
<tr><th>Different phases of treatment</th><th colspan="2"></th></tr>
<tr><td rowspan="2">Breast Cancer Women before any cancer therapy</td><td colspan="2">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 of teeth for pulpal and periapical pathologies (pulp sensitivity tests)
• Oral Prosthesis should be checked
• Periodontal index evaluation
2. Radiograph Examinations
3. Treatment protocol
Treatment planning is guided by the dental issue's urgency, available time for treatment</td></tr>
<tr><td>Full 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</td><td>Partial dental clearance protocol
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 lesions≥ 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</td></tr>
</table>

	• 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.	• accordingly • Modify, disassemble, or replace fixed prosthesis with large or symptomatic caries 3.6. Extraction: • Extraction at least 1 week before chemotherapy • Prescription antibiotics
Breast Cancer Women in the Pre-treatment Phase	**1. Oral Examination and Patient Education** 1.1. Perform a thorough oral examination, and 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 starting using ARDs) 2.2. Implant surgery and preimplant bone surgery are contraindications 2.3. Other non-invasive dental procedures such as Restorative dentistry, Endodontic treatment(pay attention to avoid over or under-filled canals), and non-surgical Periodontal treatments are indicated and do 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 and 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	
Breast Cancer Women in-treatment Phase	**1. Oral Examination and Patient Education** 1.1. Perform a thorough oral examination, and 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 cases) • 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 anesthesia 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 a rubber dam and pay attention to position clamps.
- Avoid vasoconstricting anesthetic.
- 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 those in the early stage of cancer
- Rinse with CHX mouthwash 0,12% or 0.2% for two or four times 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:

I.Removable Prosthesis:

- Schedule check-ups every 4 months.
- Recommend not wearing dentures for 8-12 hours per day, especially during the night.

II.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

Breast Cancer Women with MRONJ	Stage 0	Stage 1	Stage 2	Stage 3
	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 of 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 antimicrobial mouth rinses and antibiotic 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 of 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(IV/oral) 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 of bone **2. Surgical treatments:** 2.1. Segmental resection for mandible 2.2. Partial infrastructure maxillectomy

REFERENCES

1. Slepicka PF, Cyrill SL, dos Santos CO. Pregnancy and Breast Cancer: Pathways to Understand Risk and Prevention. Vol. 25, Trends in Molecular Medicine. Elsevier Ltd; 2019. p. 866–81.

2. Van Acker HH, Anguille S, Willemen Y, Smits EL, Van Tendeloo VF. Bisphosphonates for cancer treatment: Mechanisms of action and lessons from clinical trials. Vol. 158, Pharmacology and Therapeutics. Elsevier Inc.; 2016. p. 24–40.

3. Hallmer F, Bjarnadottir O, Götrick B, Malmström P, Andersson G. Incidence of and risk factors for medication-related osteonecrosis of the jaw in women with breast cancer with bone metastasis: a population-based study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Sep 1;130(3):252–7.

4. Shapiro CL. Bone-modifying Agents (BMAs) in Breast Cancer. Vol. 21, Clinical Breast Cancer. Elsevier Inc.; 2021. p. e618–30.

5. Goldvaser H, Amir E. Role of Bisphosphonates in Breast Cancer Therapy. Vol. 20, Current Treatment Options in Oncology. Springer New York LLC; 2019.

6. Reyes C, Hitz M, Prieto-Alhambra D, Abrahamsen B. Risks and Benefits of Bisphosphonate Therapies. J Cell Biochem. 2016 Jan 1;117(1):20–8.

7. Mirelli C, Marino S, Bovio A, Pederielli S, Dall'agnola C, Gianni AB, et al. Medication-Related Osteonecrosis of the Jaw in Dental Practice: A Retrospective Analysis of Data from the Milan Cohort. Dent J (Basel). 2022 May 1;10(5).

8. Mauceri R, Coppini M, Attanasio M, Bedogni A, Bettini G, Fusco V, et al. MRONJ in breast cancer patients under bone modifying agents for cancer treatment-induced bone loss (CTIBL): a multi-hospital-based case series. BMC Oral Health. 2023 Dec 1;23(1).

9. Boston B, Ipe D, Capitanescu B, Gresita A, Hamlet S, Love R, et al. Medication-related osteonecrosis of the jaw: A disease of significant importance for older patients. Vol. 71, Journal of the American Geriatrics Society. John Wiley and Sons Inc; 2023. p. 2640–52.

10. Soares AL, Simon S, Gebrim LH, Nazário ACP, Lazaretti-Castro M. Prevalence and risk factors of medication-related osteonecrosis of the jaw in osteoporotic and breast cancer patients: a cross-sectional study. Supportive Care in Cancer. 2020 May 1;28(5):2265–71.

11. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures. Vol. 2022, BioMed Research International. Hindawi Limited; 2022.

12. Dall GV, Britt KL. Estrogen effects on the mammary gland in early and late life and breast cancer risk. Vol. 7, Frontiers in Oncology. Frontiers Media S.A.; 2017.

13. 13. Moloney BM ODAESKMJ. Breast Cancer Detection-A Synopsis of Conventional Modalities and the Potential Role of Microwave Imaging. Diagnostics (Basel). 2022 Feb 14;

14. 14. Otto S ASFRESROBETMPCEMM (Kaunas). . Infection as an Important Factor in Medication-Related Osteonecrosis of the Jaw (MRONJ). 2021 May;

15. Tsang JYS, Tse GM. Molecular Classification of Breast Cancer [Internet]. 2019. Available from: http://journals.lww.com/anatomicpathology

16. Rakha EA, Tse GM, Quinn CM. An update on the pathological classification of breast cancer. Vol. 82, Histopathology. John Wiley and Sons Inc; 2023. p. 5–16.

17. Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. Vol. 8, Breast Care. S. Karger AG; 2013. p. 149–54.

18. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, et al. Breast cancer: Biology, biomarkers, and treatments. Vol. 84, International Immunopharmacology. Elsevier B.V.; 2020.

19. Trayes KP, Cokenakes SEH. Breast Cancer Treatment. Am Fam Physician. 2021 Aug 1;104(2):171–8.

20. He Z, Chen Z, Tan M, Elingarami S, Liu Y, Li T, et al. A review on methods for diagnosis of breast cancer cells and tissues. Vol. 53, Cell Proliferation. Blackwell Publishing Ltd; 2020.

21. O'Sullivan CC, Loprinzi CL, Haddad TC. Updates in the Evaluation and Management of Breast Cancer. Vol. 93, Mayo Clinic Proceedings. Elsevier Ltd; 2018. p. 794–807.

22. Suarez-Almazor ME, Herrera R, Lei X, Chavez-MacGregor M, Zhao H, Giordano SH. Survival in older women with early stage breast cancer receiving low-dose bisphosphonates or denosumab. Cancer. 2020 Sep 1;126(17):3929–38.

23. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant denosumab in breast cancer (ABCSG-18): A multicentre, randomised, double-blind, placebo-controlled trial. The Lancet. 2015 Aug 1;386(9992):433–43.

24. Coleman R, Finkelstein DM, Barrios C, Martin M, Iwata H, Hegg R, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020 Jan 1;21(1):60–72.

25. Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast cancer, version 3.2020. JNCCN Journal of the National Comprehensive Cancer Network. 2020 Apr 1;18(4):452–78.

26. Fu PA, Shen CY, Yang S -R, Lee CH, Chen HW, Lai ECC, et al. Long-term use of denosumab and its association with skeletal-related events and osteonecrosis of the jaw. Sci Rep. 2023 Dec 1;13(1).

27. O'Carrigan B, Wong MHF, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Vol. 2017, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2017.

28. Poon M, Zeng L, Zhang L, Lam H, Emmenegger U, Wong E, et al. Incidence of Skeletal-related Events Over Time from Solid Tumour Bone Metastases Reported in Randomised Trials Using Bone-modifying Agents. Clin Oncol. 2013 Jul;25(7):435–44.

29. Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO Clinical Practice Guidelines †. Annals of Oncology. 2020 Dec 1;31(12):1650–63.

30. Poznak C Van, Somerfield MR, Barlow WE, Biermann JS, Bosserman LD, Clemons MJ, et al. JOURNAL OF CLINICAL ONCOLOGY Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol [Internet]. 2017;35:3978–86. Available from: https://doi.org/10.1200/JCO.2017.

31. Puppo M, Valluru MK, Clézardin P. MicroRNAs and Their Roles in Breast Cancer Bone Metastasis. Vol. 19, Current Osteoporosis Reports. Springer; 2021. p. 256–63.

32. Jordt N, Kjærgaard KA, Thomsen RW, Borgquist S, Cronin-Fenton D. Breast cancer and incidence of type 2 diabetes mellitus: a systematic review and meta-analysis. Vol. 202, Breast Cancer Research and Treatment. Springer; 2023. p. 11–22.

33. Huang JF, Shen J, Li X, Rengan R, Silvestris N, Wang M, et al. Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study. Ann Transl Med. 2020 Apr;8(7):482–482.

34. Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS. Journal of Clinical Endocrinology and Metabolism. 2022 May 1;107(5):1441–60.

35. Dalle Carbonare L, Mottes M, Valenti MT. Medication-related osteonecrosis of the jaw (MRONJ): Are antiresorptive drugs the main culprits or only accomplices? the triggering role of vitamin d deficiency. Vol. 13, Nutrients. MDPI AG; 2021. p. 1–14.

36. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. Vol. 80, Journal of Oral and Maxillofacial Surgery. W.B. Saunders; 2022. p. 920–43.

37. Chukir T, Liu Y, Farooki A. Antiresorptive agents' bone-protective and adjuvant effects in postmenopausal women with early breast cancer. Vol. 85, British Journal of Clinical Pharmacology. Blackwell Publishing Ltd; 2019. p. 1125–35.

38. Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. Vol. 399, The Lancet. Elsevier B.V.; 2022. p. 1080–92.

39. Foroni C, Milan M, Strina C, Cappelletti M, Fumarola C, Bonelli M, et al. Pure anti-tumor effect of zoledronic acid in naïve bone-only metastatic and locally advanced breast cancer: Proof from the "biological window therapy." Breast Cancer Res Treat. 2014;144(1):113–21.

40. Solomayer EF, Gebauer G, Hirnle P, Janni W, Lück HJ, Becker S, et al. Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients. Annals of Oncology. 2012;23(9):2271–7.

41. Insalaco L, Di Gaudio F, Terrasi M, Amodeo V, Caruso S, Corsini LR, et al. Analysis of molecular mechanisms and anti-tumoural effects of zoledronic acid in breast cancer cells. J Cell Mol Med. 2012;16(9):2186–95.

42. Dunphy L, Salzano G, Gerber B, Graystone J. Medication-related osteonecrosis (MRONJ) of the mandible and maxilla. BMJ Case Rep. 2020 Jan 5;13(1).

43. Fda. HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. Available from: www.fda.gov/medwatch.

44. Lu J, Hu D, Zhang Y, Ma C, Shen L, Shuai B. Current comprehensive understanding of denosumab (the RANKL neutralizing antibody) in the treatment of bone metastasis of malignant tumors, including pharmacological mechanism and clinical trials. Vol. 13, Frontiers in Oncology. Frontiers Media S.A.; 2023.

45. Okamoto K, Takayanagi H. Osteoimmunology. Cold Spring Harb Perspect Med. 2019 Jan 1;9(1).

46. Luan X, Lu Q, Jiang Y, Zhang S, Wang Q, Yuan H, et al. Crystal Structure of Human RANKL Complexed with Its Decoy Receptor Osteoprotegerin. The Journal of Immunology. 2012 Jul 1;189(1):245–52.

47. Kendler DL CFSRFS. Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review. 2022 Jan;

48. Ikebuchi Y, Aoki S, Honma M, Hayashi M, Sugamori Y, Khan M, et al. Coupling of bone resorption and formation by RANKL reverse signalling. Nature. 2018 Sep 13;561(7722):195–200.

49. Gül G, Sendur MAN, Aksoy S, Sever AR, Altundag K. A comprehensive review of denosumab for bone metastasis in patients with solid tumors. Vol. 32, Current Medical Research and Opinion. Taylor and Francis Ltd; 2016. p. 133–45.

50. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. Vol. 30, Journal of Bone and Mineral Research. John Wiley and Sons Inc.; 2015. p. 3–23.

51. Kuehn S, Scariot R, Elsalanty M. Medication-Related Osteonecrosis: Why the Jawbone? Vol. 11, Dentistry Journal. MDPI; 2023.

52. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. Vol. 6, Journal of International Society of Preventive and Community Dentistry. Wolters Kluwer (UK) Ltd.; 2016. p. 97–104.

53. Howie RN, Borke JL, Kurago Z, Daoudi A, Cray J, Zakhary IE, et al. A Model for Osteonecrosis of the Jaw with Zoledronate Treatment following Repeated Major Trauma. PLoS One. 2015 Jul 17;10(7).

54. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: A cohort study. Int J Oral Maxillofac Surg. 2012 Nov;41(11):1397–403.

55. Kang SH, Park SJ, Kim MK. The effect of bisphosphonate discontinuation on the incidence of postoperative medication-related osteonecrosis of the jaw after tooth extraction. J Korean Assoc Oral Maxillofac Surg. 2020 Feb 1;46(1):78–83.

56. Otto S, Aljohani S, Fliefel R, Ecke S, Ristow O, Burian E, et al. Infection as an important factor in medication-related osteonecrosis of the jaw (Mronj). Medicina (Lithuania). 2021;57(5).

57. Elsayed R, Kurago Z, Cutler CW, Arce RM, Gerber J, Celis E, et al. Role of dendritic cell-mediated immune response in oral homeostasis: A new mechanism of osteonecrosis of the jaw. FASEB Journal. 2020 Feb 1;34(2):2595–608.

58. AlDhalaan NA, BaQais A, Al-Omar A. Medication-related Osteonecrosis of the Jaw: A Review. Cureus. 2020 Feb 11;

59. Ewald F, Wuesthoff F, Koehnke R, Friedrich RE, Gosau M, Smeets R, et al. Retrospective analysis of bacterial colonization of necrotic bone and antibiotic resistance in 98 patients with medication-related osteonecrosis of the jaw (MRONJ). Clin Oral Investig. 2021 May 1;25(5):2801–9.

60. Schiodt M, Otto S, Fedele S, Bedogni A, Nicolatou-Galitis O, Guggenberger R, et al. Workshop of European task force on medication-related osteonecrosis of the jaw—Current challenges. In: Oral Diseases. Blackwell Publishing Ltd; 2019. p. 1815–21.

61. Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, et al. Nonsurgical Management of Medication-Related Osteonecrosis of the Jaws Using Local Wound Care. Journal of Oral and Maxillofacial Surgery. 2018 Nov 1;76(11):2332–9.

62. Lončar Brzak B, Horvat Aleksijević L, Vindiš E, Kordić I, Granić M, Vidović Juras D, et al. Osteonecrosis of the Jaw. Vol. 11, Dentistry Journal. MDPI; 2023.

63. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. Vol. 69, Cancer Treatment Reviews. W.B. Saunders Ltd; 2018. p. 177–87.

64. Deepigaa M, Arvind M. Clinical Practice Guidelines in Dental Management of Medication Related Osteonecrosis of Jaw (MRONJ). Journal of Research in Medical and Dental Science 2021 [Internet]. 2021;9(1):128–33. Available from: www.jrmds.in

65. Kim JE, Yoo S, Choi SC. Several issues regarding the diagnostic imaging of medication-related osteonecrosis of the jaw. Imaging Sci Dent. 2020 Dec 1;50(4):273–9.

66. Tocaciu S, Breik O, Lim B, Angel C, Rutherford N. Diagnostic dilemma between medication-related osteonecrosis and oral squamous cell carcinoma in a mandibular lytic lesion. British Journal of Oral and Maxillofacial Surgery. 2017 Nov 1;55(9):e53–7.

67. Kuchuk I, Mazzarello S, Butterfield K, Appleton A, Addison CL, Clemons M. Oral care and the use of bone-targeted agents in patients with metastatic cancers: A practical guide for dental surgeons and oncologists. Vol. 2, Journal of Bone Oncology. Elsevier GmbH; 2013. p. 38–46.

68. Kün-Darbois JD, Fauvel F. Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management. Vol. 105, Morphologie. Elsevier Masson s.r.l.; 2021. p. 170–87.

69. Kuroshima S, Sasaki M, Sawase T. Medication-related osteonecrosis of the jaw: A literature review. Vol. 61, Journal of Oral Biosciences. Japanese Association for Oral Biology; 2019. p. 99–104.

70. Kün-Darbois JD, Libouban H, Mabilleau G, Pascaretti-Grizon F, Chappard D. Bone mineralization and vascularization in bisphosphonate-related osteonecrosis of the jaw: an experimental study in the rat. Clin Oral Investig. 2018 Dec 1;22(9):2997–3006.

71. Lorenzo-pouso AI, Bagán J, Bagán L, Gándara-vila P, Chamorro-petronacci CM, Castelo-baz P, et al. Medication-related osteonecrosis of the jaw: A critical narrative review. Vol. 10, Journal of Clinical Medicine. MDPI; 2021.

72. Gao S yong, Lin R bang, Huang S hui, Liang Y jie, Li X, Zhang S en, et al. PDGF-BB exhibited therapeutic effects on rat model of bisphosphonate-related osteonecrosis of the jaw by enhancing angiogenesis and osteogenesis. Bone. 2021 Mar 1;144.

73. Gkouveris I, Hadaya D, Soundia A, Bezouglaia O, Chau Y, Dry SM, et al. Vasculature submucosal changes at early stages of osteonecrosis of the jaw (ONJ). Bone. 2019 Jun 1;123:234–45.

74. Basso FG, Pansani TN, Soares DG, Cardoso LM, Hebling J, de Souza Costa CA. Influence of bisphosphonates on the adherence and metabolism of epithelial cells and gingival fibroblasts to titanium surfaces. Clin Oral Investig. 2018 Mar 1;22(2):893–900.

75. de Molon RS, Hsu C, Bezouglaia O, Dry SM, Pirih FQ, Soundia A, et al. Rheumatoid Arthritis Exacerbates the Severity of Osteonecrosis of the Jaws (ONJ) in Mice. A Randomized, Prospective, Controlled Animal Study. Journal of Bone and Mineral Research. 2016 Aug 1;31(8):1596–607.

76. Wick A, Bankosegger P, Otto S, Hohlweg-Majert B, Steiner T, Probst F, et al. Risk factors associated with onset of medication-related osteonecrosis of the jaw in patients treated with denosumab. Clin Oral Investig. 2022 Mar 1;26(3):2839–52.

77. De Cicco D BCSMCGSSGABGVRDS. Medication-Related Osteonecrosis of the Jaws: A Comparison of SICMF-SIPMO and AAOMS Guidelines. Diagnostics (Basel). 2023 Jun;

78. ÅŸahin O, OdabaÅŸÄ± O, Aliyev T, Tatar B. Risk factors of medication-related osteonecrosis of the jaw: A retrospective study in a Turkish subpopulation. J Korean Assoc Oral Maxillofac Surg. 2019 Apr 30;45(2):108–15.

79. Soutome S, Otsuru M, Hayashida S, Murata M, Yanamoto S, Sawada S, et al. Relationship between tooth extraction and development of medication-related osteonecrosis of the jaw in cancer patients. Sci Rep. 2021 Dec 1;11(1).

80. Avishai G, Muchnik D, Masri D, Zlotogorski-Hurvitz A, Chaushu L. Minimizing MRONJ after Tooth Extraction in Cancer Patients Receiving Bone-Modifying Agents. J Clin Med. 2022 Apr 1;11(7).

81. Mauceri R, Panzarella V, Carbone MI, Oteri G, Marcianó A, Di Fede O, et al. Open Peer Review on Qeios Histological findings of osteonecrosis spotted prior to tooth extractions. Should we consider tooth extraction still the main trigger event? Available from: https://doi.org/10.32388/JK459H.2

82. Pichardo SEC, van der Hee JG, Fiocco M, Appelman-Dijkstra NM, van Merkesteyn JPR. Dental implants as risk factors for patients with medication-related osteonecrosis of the jaws (MRONJ). British Journal of Oral and Maxillofacial Surgery. 2020 Sep 1;58(7):771–6.

83. Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO Clinical Practice Guidelines †. Annals of Oncology. 2020 Dec 1;31(12):1650–63.

84. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012 Nov;48(16):3082–92.

85. Gnant M, Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Mar 1;20(3):339–51.

86. Sim IW, Sanders KM, Borromeo GL, Seymour JF, Ebeling PR. Declining incidence of medication-related osteonecrosis of the jaw in patients with cancer. Journal of Clinical Endocrinology and Metabolism. 2015 Oct 1;100(10):3887–93.

87. Singh N, Surface L. Dental Management of Medication-Related OSTEONECROSIS of the JAW: WHILE RARE, THIS PATHOLOGY HAS DEVASTATING EFFECTS ON PATIENT HEALTH AND QUALITY OF LIFE.

88. Ottesen C, Schiodt M, Gotfredsen K. Efficacy of a high-dose antiresorptive drug holiday to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ): A systematic review. Vol. 6, Heliyon. Elsevier Ltd; 2020.

89. Hasegawa T, Ueda N, Yamada S, Kato S, Iwata E, Hayashida S, et al. Denosumab-related osteonecrosis of the jaw after tooth extraction and the effects of a short drug holiday in cancer patients: a multicenter retrospective study. Osteoporosis International. 2021 Nov 1;32(11):2323–33.

90. Aljohani S, Gaudin R, Weiser J, Tröltzsch M, Ehrenfeld M, Kaeppler G, et al. Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series. Journal of Cranio-Maxillofacial Surgery. 2018 Sep 1;46(9):1515–25.

91. Hoefert S, Yuan A, Munz A, Grimm M, Elayouti A, Reinert S. Clinical course and therapeutic outcomes of operatively and non-operatively managed patients with denosumab-related osteonecrosis of the jaw (DRONJ). Journal of Cranio-Maxillofacial Surgery. 2017 Apr 1;45(4):570–8.

92. Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Vol. 127, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. Mosby Inc.; 2019. p. 117–35.

93. He L, Sun X, Liu Z, Qiu Y, Niu Y. Pathogenesis and multidisciplinary management of medication-related osteonecrosis of the jaw. Vol. 12, International Journal of Oral Science. Springer Nature; 2020.

94. Scribante A, Ghizzoni M, Pellegrini M, Pulicari F, Spadari F. Laser Devices and Autologous Platelet Concentrates in Prevention and Treatment of Medication-Related Osteonecrosis of the Jaws: A Systematic Review. Vol. 59, Medicina (Lithuania). MDPI; 2023.

95. Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L, et al. The dental management of patients at risk of medication-related osteonecrosis of the jaw: New paradigm of primary prevention. Vol. 2018, BioMed Research International. Hindawi Limited; 2018.

96. Yong CW, Robinson A, Hong C. Dental Evaluation Prior to Cancer Therapy. Vol. 3, Frontiers in Oral Health. Frontiers Media SA; 2022.

97. Prof. G. Campisi – Professore Straordinario - Dirigente Medico I Livello Dott. O. Di Fede - Ricercatore-. PROMaF protocol: Prevention and research on Medication relate Osteonecrosis of the Jaws, . 2014 Dec;

98. A. Bedogni GCVF and AA. Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossamascellari associata a bisfosfonati e sua prevenzione," SICMF - SIPMO. 2013;

99. Mauceri R, Panzarella V, Pizzo G, Oteri G, Cervino G, Mazzola G, et al. Platelet-Rich Plasma (PRP) in dental extraction of patients at risk of bisphosphonate-related osteonecrosis of the jaws: A two-year longitudinal study. Applied Sciences (Switzerland). 2020 Jul 1;10(13).

100. Parise GK, Costa BN, Nogueira ML, Sassi LM, Schussel JL. Efficacy of fibrin-rich platelets and leukocytes (L-PRF) in tissue repair in surgical oral procedures in patients using zoledronic acid—case–control study. Oral Maxillofac Surg. 2023 Sep 1;27(3):507–12.

101. Moinzadeh AT, Shemesh H, Neirynck NAM, Aubert C, Wesselink PR. Bisphosphonates and their clinical implications in endodontic therapy. Vol. 46, International Endodontic Journal. 2013. p. 391–8.

102. Mosaico G, Casu C. Management and maintenance of oral health: Personalized primary prevention strategies and protocols in patients at risk of developing medication-related osteonecrosis of the jaw. INNOSC Theranostics and Pharmacological Sciences. 2024 Jan 11;0(0):1419.

103. Ministero della Salute "Dipartimento della sanit`a pubblica e dell'innovazione. Raccomandazioni per la promozione della salute orale, la prevenzione delle patologie orali e la terapia odontostomatologica nei pazienti adulti con malattia neoplastica. 2014 Jan;

104. Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, et al. Nonsurgical Management of Medication-Related Osteonecrosis of the Jaws Using Local Wound Care. Journal of Oral and Maxillofacial Surgery. 2018 Nov 1;76(11):2332–9.

105. Inchingolo AM, Malcangi G, Ferrara I, Patano A, Viapiano F, Netti A, et al. MRONJ Treatment Strategies: A Systematic Review and Two Case Reports. Vol. 13, Applied Sciences (Switzerland). MDPI; 2023.

106. Ciobanu GA, Mogoantă L, Camen A, Ionescu M, Vlad D, Staicu IE, et al. Clinical and Histopathological Aspects of MRONJ in Cancer Patients. J Clin Med. 2023 May 1;12(10).

107. Kaibuchi N, Hoshi K, Yamazaki A, Miyamoto-Sangu N, Akagi Y, Okamoto T. The progress of medication-related osteonecrosis of the jaw with conservative initial treatment: A 12-year retrospective study of 129 patients. Bone Rep. 2021 Jun 1;14.