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REVIEW PAPER

Osteonecrosis of the Jaws: An Update and Review of Literature

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Abstract

Aim To provide a concise review on risk factors, stages, pathophysiology, prevention and possible treatment options for both MRONJ and ORN individually.

Methods The review was conducted according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines. A comprehensive search of the PUBMED, Ebsco, SCOPUS, WEB OF SCIENCE and NDH for articles published up until 2021 was performed. After screening and full text analyses, 44 studies were included in this review. Definition, risk factors, etiology, symptoms, stages, pathophysiology, prevention and possible management options were explored and highlighted in this article.

Results Three studies described osteonecrosis of jaw (ONJ) in general, 15 studies described ONJ associated with radiotherapy and 26 studies described ONJ associated with medications. Both the two conditions (ORN) and (MRONJ) have relatively similar clinical presentations clearing the fact that a resemblance in clinical presentations does not necessarily denote a similar pathophysiology.

Conclusion However, various advancements have been made in the control and management of ONJ, but until and unless need for high tumoricidal doses exists, ONJ will certainly continue to remain as a clinical challenge demanding satisfactory treatment to improve the quality of life of the patient.

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Introduction

'Osteo-necrosis' is a process by which the blood flow to the living cells of the bones and bone marrow decreases and the cells die causing the bone to collapse. Initially, the term 'osteonecrosis' was used to refer to femoral head avascular necrosis in medical orthopaedics literature and eventually it was found affecting the head and neck area and termed as 'Osteonecrosis of jaw'. Two main aetiologies of osteonecrosis of jaw that has been described in the literature are medication related osteonecrosis of jaw (MRONJ) and osteoradionecrosis (ORN). However, many sources report positive correlation between MRONJ and ORN and tooth extraction and/ or alveolar trauma and infection [1, 2]. Osteoblasts, osteocytes, osteoclast, and bone lining cells play a role in coordination in replacing mature bone by new bone which is a lifelong process called bone remodelling [3, 4]. Although osteoclasts contribute to bone resorption and their differentiation plays an important role in bone healing and remodelling of all areas of the skeleton, osteonecrosis is more common in the jaw for various reasons related to the anatomical and physiological features of the jaw [3, 4]. When there is imbalance in the regulation of the process of bone metabolism, many skeletal complications including osteoporosis occurs. An epidemic of exposed bone osteonecrosis exclusively in the jaws occurred at around 1858—1906, known as 'Phossy jaw' and was linked to 'yellow phosphorous', the main ingredient used in factories that makes match [5]. Forensic evidences says that yellow phosphorous ($P4O_{10}$) gets converted into potent amino-bisphosphonate when combined with H_2O_2 and CO_2 by natural chemical reaction in the human body, which was found to be the aetiology behind the

phossy jaw [5]. Today's Bisphosphonates related osteonecrosis of jaw (BRONJ) is the 2nd epidemic of 'Phossy jaw' [5]. Bisphosphonate were first synthesized in Germany in 1865 and used to treat a number of metabolic and oncologic pathologies that contribute to the destruction of the skeletal system [6]. ONJ was also found to be related to the anti-angiogenic medication family [7–9]. They inhibit osteoclast function and differentiation and increase osteoclast apoptosis which reduces bone turnover in the affected area and reduces angiogenesis, ultimately leading to osteonecrosis [7–9]. So, to include all drugs that are effective in causing osteonecrosis of jaw, the American Association of Oral and Maxillofacial Surgery (AAOMS) renamed the term BRONJ to MRONJ considering the increasing incidence of osteonecrosis with other anti-resorptive and anti-angiogenic agents and in 2014 they also published a position paper explaining the same [10]. Also, first report about osteoradionecrosis of jaw (ORN) after radiotherapy was published by Regaud, in 1992 [2]. After that, multiple theories have been given to describe the pathophysiology of ORN among which Hypoxic-hypocellular theory and Radiation-induced fibro-optic theory are the two most accepted one [2, 11]. Definition, aetiology, clinical features, diagnosis, risk factors, pathophysiology, prevention and possible treatment options of both (ORN and MRONJ) have been discussed here.

Discussion

Osteoradionecrosis (ORN)

Radiation therapy in the management of head and neck cancer plays an important role in osteoradionecrosis (ORN) of the jaws. Incidence of ORN ranges from 20–22% and is most often noted in first 3 years after end of treatment [12]. ORN of mandible is more prevalent when compared to maxilla due to poor vascularization and dense bone of mandible relatively.Posterior region of the mandible is more commonly affected by ORN than the anterior region, because of compact and dense bone of the mandible [13]. Incidence of ORN is three times higher in dentate compared to edentulous patients due to trauma and infections from extractions and periodontal disease, respectively [14]. Risk factors associated with development of ORN are—primary site of tumour, proximity of tumour to bone, extent of mandible included in primary radiation field, state of dentition (odontogenic and periodontal disease), poor oral hygiene, radiation dose more than 60 Gy, use of brachytherapy, dental extractions, poor nutrition, concomitant chemo-radiation, acute trauma from surgical procedures to the jaw, tobacco and alcohol abuse and ill-fitting prosthesis causing chronic trauma [15] (Table 2).

ORN occurs after radiation because it changes the lumen of blood vessels, stops tissue perfusion and affects small blood vessels in the bones, leading to endarteritis with the formation of small clots. So, the bone loses its repair and remodelling capacity, and in such condition even a small external trauma causes ulceration and infection leading to bone necrosis. To explain the pathophysiology of ORN some theories have been proposed [2, 11]. According to Meyer's theory of trauma and infection, the damage facilitates the penetration of oral microflora into the irradiated bone [11]. This theory underlies the widespread use of antibiotics in surgical interventions for the treatment of ORN. Marx's pathological sequence for explaining his hypoxic-hypocellular theory—irradiation, formation of hypoxic-hypocellular, hypovascular tissue and breakdown of tissues driven by persistent hypoxia that can lead to a chronic non-healing wound [11]. This explanation laid the keystone for the treatment of ORN by using hyperbaric oxygen (HBO) therapy [11]. Radiation-induced fibro-atrophic theory is the newest theory of pathophysiology of ORN which was introduced in 2004 [2, 16]. This theory, states that the main event for the initiation and development of osteoradionecrosis is the aberrant stimulation and regulation of function of fibroblast, that results in tissue degeneration within the area which is irradiated previously [16] (Table 2).

The diagnosis of ORN is arrived at by considering a combination of certain predominant clinical signs such as ulceration of oral mucosa with exposure of necrotic bone along with symptoms of halitosis, pain, paraesthesia, altered taste sensation and food impaction in the concerned area [17] (Table 2).

Measures for prevention of ORN should be evaluated to reduce the risk of ORN—thorough dental check-ups are indicated prior to radiotherapy to rule out decayed tooth with poor prognosis, periodontal disease or with existing infections; dentures should be regularly checked for pressure areas and adjusted to avoid excessive pressure points that may cause pressure ulcers; removal of all mandibular molars in field of > 60 Gy unless the patient has excellent oral hygiene, daily application of topical fluoride, xerostomia patients should be provided with neutral PH saliva substitutes and close follow ups with the patient should be maintained to rule out ORN of the jaws [18]. Advancement in the field of radiation therapy in the form of Intensity Modulated Radiation Therapy (IMRT) have led to reduction in the incidence and severity of ORN as compared to conventional radiotherapy [19]. Based on the pathophysiology of ORN new prevention protocols have been given. Pentoxifylline 400 mg twice daily for 8 weeks with tocopherol 1000 IU, starting a week before the any surgical procedure can be given as prescription [15] (Table 2).

Management of ORN includes conservative as well as surgical measures (Table 2). Conservative treatment

includes mouth rinses (saline rinses, $NaHCO_3$ or 0.02% chlorhexidine) and systematic antibiotics along with gentle removal of the sequestrum over the lesion additionally can help in management of early stage of ORN [20]. The new therapeutic regime that includes pentoxifylline and tocopherol acts synergistically and act as a potent anti-fibrotic agent which helps to reverse changes related to radiation-induced fibrosis ultimately preventing its conversion to ORN [20]. Hyperbaric Oxygen Therapy (HBO) was described in 1973 as an adjunct to the treatment of ORN. HBO increases tissue oxygen tension and promotes collagen synthesis, angiogenesis, and epithelization [21]. Wilford Hall HBO osteoradionecrosis protocol given by Marx, stages ORN in its reaction to its HBO management protocol [2], [21]

- Stage I—30 consecutive exposures—wound shows no improvement clinically—10 more exposures (total of 40 exposures)—if wound fails to heal after 3 months—disease advanced to stage II.
- Stage II—alveolar sequestrectomy to remove exposed bone and 20 HBO exposures are given (60 exposures in total)—if wound fail to heal—condition is progressed to Stage III
- Stage III—failure of stage II, pathological fracture, formation of orocutaneous fistula.

According to Marx, HBO therapy alone cannot treat osteonecrotizing bone and suggested combining surgery and HBO therapy [22]. Recommended management includes 30 HBO exposure along with resection to bleeding bone followed by reconstruction and then additional 10 exposures of HBOT. If healing fails, surgery is repeated followed by 10 more HBO treatments [22]. Ultrasound was introduced as a treatment option for ORN in 1992 by Haris, which was found to improve the blood flow to muscle, induce angiogenesis and healing of ischaemic ulcers. Protocol advised was 40e 50v (10 min) ultrasound sessions [23]. Post-op sequels such as bone loss and soft tissue defects cannot be avoided after aggressive surgical procedure, so the reconstruction after such complications is important in view of maintaining the functions and aesthetics [24]. To achieve the superior results after traditional grafting techniques (replacement of dead bone with vascularized bone containing flaps), angiogenic cytokines and bone substitutes are introduced [24].

The current researches approve the theory of radiation-induced fibro-atrophic process in the pathogenesis of ORN in which free reactive oxygen species plays the role and can be reduced by the administration of new therapeutic regime which include administration of pentoxifylline with tocopherol [15].

Medication Related Osteonecrosis of Jaw (MRONJ)

MRONJ, has become an arising disease in recent years because of highly prescribed anti-resorptive as well as anti-angiogenic drugs to treat oncologic and osteoporotic patients. The incidence of MRONJ is reported as 1% in cancer patients and 0.1% in patients with metabolic bone disease and it is more common following dental extractions [25]. MRONJ is more common in mandible (73%) than maxilla (22.5%) and in areas with bone prominences (tori, exostoses, and the mylohyoid ridge) with thin overlying mucosa [26]. Risk factors of MRONJ are many—I.V Bisphosphonates (BPs), zoledronate, dental extractions, periodontal disease, glucocorticoid, chemotherapy, smoking and obesity are the most common [9, 10, 12, 25]. Anti-resorptive drugs (Bisphosphonate and Denosunab) are monoclonal antibodies acting against receptor activator of neuclear factor kappa-B ligand (RANKL) which are found to be causing MRONJ in fewer doses [9, 12]. Anti-angiogenic drugs (Sunitinib and Bevacizumab) are humanized monoclonal antibodies directed against several activated Receptors Tyrosine Kinase (i.e. vascular endothelial growth factor receptor) [9, 12]. Anti-angiogenic therapy is used in the management of malignancies involving ovary, metastatic renal cell cancer, breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer and glioblastoma multiforme [27]. There is a significant relationship between duration of exposure and development of MRONJ of anti-angiogenic medication administered with anti-resorptive medication [27]. Few case reports have also found an association between ONJ and isolated use of infliximab (chimeric human-murine IgG1 monoclonal antibody) and sorafenib (tyrosine kinase inhibitor used as anti-angiogenic) [28, 29]. Steroid and methotrexate are the newly added drugs that may be associated with MRONJ [30]. Concomitant use of BPs or denosumab along with corticosteroids increases the risk of developing ONJ. Methotrexate(cytotoxic medication) is a drug which is indicated in the treatment of a number of solid tumours, haematological malignancies and rheumatoid arthritis is also found to cause ONJ if used concomitantly along with BPs/denosumab [30]. Some systemic and local risk factors in the development of MRONJ are diabetes and anaemia have also been found [30] (Table 2).

Many hypotheses have been suggested for pathophysiology of MRONJ (Table 2)

(1) Imbalance in osteoblasts and osteoclasts in bone remodelling—osteoclast help in bone resorption and the absorbed bone is replaced by fresh bone produced by osteoblast [31]. Apoptosis of osteoclast and inhibition of its differentiation and function resulting in decrease in bone resorption are the actions of BPs and other anti-resorptive drugs [31, 32]. Osteoclasts in the

jaw are more sensitive to BPs than those in the long bones due to presence of less amount of fat than other bones [31, 32]. Though BPs are successfully used to treat many bone diseases like paget's disease, osteoporosis but it can affect the survival of osteoblasts and their progenitor cells if it reaches its toxic level within a bone [31–33]. Also in a recent study, it was found that treatment with BPs reduces the expression of BMP-2 (bone morphogenicprotein-2) which has a major role in bone remodelling, development, and osteoblast differentiation [34]. There is suppression of early differentiation marker Type 1 collagen, intermediate differentiation marker such as osterix and alkaline phosphatase (ALP), and the late differentiation marker osteocalcin [34]. BP treatment alters the RANKL-OPG complex which stimulates osteoclasts via its receptor RANK [31, 34]. Recently developed drug Denosumab inhibit osteoclasts by blocking RANKL-RANK interaction and thus decrease bone resorption [35]. As a result, decrease in bone turnover occurs and the expression of RANK is altered by multiple signalling pathways, giving rise to accumulation of non-renewed and hypermineralized bone [35]. So, it was found that the signalling pathway of RANK/RANKL/OPG is triggered in MRONJ subjects [35].

(2) Inhibition of angiogenesis—angiogenesis is regeneration of new blood vessels facilitated by VEGF which is a very important process for viability of body organs including bones. Seeing that the cancer cell-staking advantage of angiogenesis intumour invasion and metabolism, anti-angiogenic drugs have been introduced [7, 12]. In early 2000, avascular necrosis was given as one of the early theories of MRONJ. In addition, on a clinical level, mandible was found to be more prone to avascular necrosis than maxilla due to lower vascularity and dense compact bone of mandible [34]. Role of zoledronic acid in decreasing the level of VEGF has also been reported in literature [34].

(3) Immune system dysfunction—bone remodelling is closely linked to immune system. Neutrophils helps in defence mechanism to promote wound healing following non-infectious injuries and this ability of neutrophils is altered by MRONJ [34, 36]. BPs causes an inhibitory effect and reduce the liability and differentiation capacity of the macrophage, leading to impaired wound healing in MRONJ affected areas [35, 36]. Drug Denosumab inhibits the RANK-RANKL interaction which being normal increases the production of proinflammatory cytokines and reduces monocytes, resulting in MRONJ [35, 36]. Expression of interleukins (IL6 andIL-36 α) are elevated following treatment with BPs which are related to immune response involving lymphocytes and macrophages [35, 36]. These interleukins are found to be activating STAT 3 pathway and TGF-β pathway, therefore giving evidences of multiple signalling pathway involving in pathogenesis of MRONJ [34, 35].

(4) Soft tissue toxicity—in few literatures it has been found that the BPs are also related to the soft tissue toxicity with mucosal ulceration being the initial pathologic event occurring in MRONJ. It has been found that alteration in TGF-β1 signalling after BP treatment may lead to change in oral mucosal tissue [37].

(5) Infection/inflammation—in the biopsied specimens of necrotic bone removed from the patients with ONJ, various bacteria have been found [34]. In some studies, it was found that MRONJ occurs following extraction of teeth in patient's having periodontal or periapical infections, while some studies found that patient having periapical and periodontal infection can suffer from MRONJ with or without extraction because number and function of osteoclast are modified by infection [34]. A key factor that is found in thepathogenesis of MRONJ is the presence of IL-36 in the gingival crevicular fluid in the patients with with periodontal disease which is indirectly related to TGF-beta signalling pathway [34].

(6) Other factors relating to pathogenesis of MRONJ are—systemic disease like rheumatoid arthritis, diabetes mellitus, which are in turn related to other pathways of injuries such as microvascular ischaemia and reduced bone remodelling [38]. Some literature also supported genetic factors related to pathogenesis of MRONJ such as single nucleotide polymorphisms (SNPs) which are associated with certain metabolic bone disease [39, 40].

MRONJ shows an area of yellowish white exposed necrotic bone with smooth or ragged surfaces unilaterally (mostly) and bilaterally (less frequently) or sometimes multifocal on clinical diagnosis [41]. Some criteria have been given to confirm the diagnosis of MRONJ—presence of any exposed bone that can be explored through extraoral or intraoral fistula in the oral and maxillofacial area for eight weeks and there is positive history of treatment with anti-angiogenic or anti-resorptive drugs but not with any radiation therapy [12] (Table 1). A staging system of MRONJ is given depending upon which management of MRONJ is decided [12]

Prevention of MRONJ includes—prophylactic dental intervention before anti-resorptive therapy, dental radiographs of cancer patients before receiving anti-resorptive medications, patient's education, application of fluoride and chlorhexidine rinses and controlling risk factors such as smoking and alcohol (Table 2). These have been found to reduce the risk of MRONJ by 50% [42].

Table 1 Staging system of MRONJ as per AAOMS [12]

MRONJ staging	
At risk category	No obvious exposed/necrotic bone in patients who have been treated with either anti-resorptive or anti-angiogenic agents
Stage 0	Indefinite clinical findings and symptoms such as jaw pain or osteosclerosis but no evidence of exposed bone clinically
Stage 1	Exposed, necrotic bone or fistula that can be explored to bone. No symptoms or evidence of infection
Stage 2	Exposed, necrotic bone or fistula that can be explored to bone, associated with infection, pain, and erythema in areas of the exposed bone. Pus drainage may also be present
Stage 3	Exposed, necrotic bone or fistula that can be explored to bone in patients with pain, infection, and one or more of the following: extra-oral fistula, pathologic fracture, oral antral communication or osteolysis extending to the inferior border or sinus floor

Established diagnosis of MRONJ can be managed by both with non-surgical conservative therapy and surgical therapy [10] (Table 2). If the MRONJ condition is between stage 0 and stage 1 (and even for certain stage 2 cases), management approach can be conservative which includes, maintenance of optimum oral hygiene, regular dental examination,

Table 2 Summery of ORN and MRONJ [2, 11–44]

	ORN	MRONJ
Incidence	20–22%	1% in cancer patients and 0.1% in patients with metabolic bone disease
	More prevalent in Maxilla than Mandible,	
	Posterior mandible is more commonly affected than anterior	
	More common in dentate than edentulous patient	More common after denta l extractions and prevalent in maxilla and in areas with bone prominences with thin over overlying mucosa
	Primary site and proximity of tumour,	I.V Bisphosphonates
	Extent of mandible included in the primary radiation field,	Dental extractions
	State of dentition, poor oral hygiene,	Periodontal disease
	Radiation dose > 60 Gy, use of brachytherapy,	Glucocorticoid
	Dental extractions,	Chemotherapy
	Poor nutrition,	Smoking
	Concomitant chemo-radiation,	Obesity
	Acute trauma to jaw,	Anti-angiogenic drugs
	Ill-fitting tissue bone prosthesis,	Steroid and methotrexate concomitantly used with anti-resorptive drugs
Risk factors	Tobacco and alcohol use	Systemic and local factors like diabetes and anaemia
Pathophysiology	Meyer's theory of trauma and infection	Imbalance in osteoblasts and osteoclasts in bone remodelling
	Marx pathological hypoxic-hypocellular theory	Inhibition of angiogenesis
	Radiation-induced fibro-atrophic theory	Immune system dysfunction
		Soft tissue toxicity
		Infection/inflammation
		Systemic disease like Rheumatoid arthritis, Diabetes Mellitus
Diagnosis	Ulceration of oral mucosa with exposure of necrotic bone	Yellowish white exposed necrotic with smooth/ ragged surfaces unilaterally mostly and bilaterally less frequently or multifocal
	Halitosis	
	Pain	
	Paraesthesia	Bone explored through extra-oral or intraoral fistula for 8 weeks and positive history of treatment with anti-angiogenic/ anti-resorptive drugs but not radiation therapy
	Altered taste sensation	
	Food impaction	
		Pathologic fracture
		Pain
		Infection
		Pus discharge

Table 2 (continued)

	ORN	MRONJ
Prevention	Regular dental assessment prior to radiotherapy	Prophylactic dental intervention before anti-resorptive therapy
	Dentures should be regularly checked for excessive pressure points	Dental radiographs of cancer patients before receiving anti-resorptive therapy
	Removal of all teeth in the field of > 60 Gy	Patient's education
	Daily application of topical fluoride	Application of fluoride and chlorhexidine rinses and controlling risk factors such as smoking and alcohol
	Neutral PH saliva substitutes for xerostomia patients	
	IMRT reduces the incidence and severity of ORN	
	Pentoxifylline 400 mg daily for 8 weeks with	
	Tocopherol 1000 IU, started a week before any surgical procedure	
Management	*Conservative* Mouth rinses (saline,	*Non-Surgical Conservative*
	$NaHCO_3$ or 0.02% chlorhexidine)	Stage 0 and stage 1 –conservative maintenance of optimum oral hygiene, regular dental examination, anti-microbial mouth rinse, and systemic antibiotics with non-surgical sequestrectomy additionally
	Systemic antibiotics, tobacco, and alcohol restrictions	
	Restriction of denture use	
	In ADDITION—gentle removal of the sequestrum over the lesion	
	New therapeutic regime—pentoxifylline 400 mg and Tocopherol 1000 IU	Symptomatic patients (stage 2 and stage 3)—removal of necrotic bone + anti-microbial agent s (topical or systemic) like Amoxycillin/ Amoxiclav, metrogyl, Quinolone, Clindamycin, and Erythromycin
	HBOT as proposed by Marx	
	Ultrasound sessions 40 e 50v (10 min) to produce vascularity	If does not respond to Conservative therapy then –
	Surgical	*Surgical*
	Debridement	Debridement with proper elevation and mobilization of full thickness mucoperiosteal flap
	Sequestrectomy	
	Excision, decortication, and reconstruction (traditional grafting techniques, angiogenic cytokines and bone substitutes)	Laser assisted surgical debridement
		Administration of ozone oil
		PRP

anti-microbial mouth rinse and systemic antibiotics in addition to non-surgical sequestrectomy [10, 12]. In symptomatic patients along with removal of necrotic bone, careful selection of anti-microbial agents (topical and/ or systemic) is recommended [10, 12]. Antibiotic groups such as Amoxicillin and/ amoxiclav, metronidazole, quinolones, clindamycin and erythromycin can be given. In addition to systemic antibiotics, chlorhexidine mouthwash can be prescribed in order to reduce bacterial load in the oral cavity and this conservative therapy can be continued up to several weeks [10, 12]. If the patient with MRONJ does not respond to conservative therapy, surgery is indicated [12, 43]. Aggressive surgery is done by elevating a full thickness mucoperiosteal flap revealing the whole region of the exposed bone and beyond the healthy margins with proper mobilization and closure to accomplish tension free mucosal healing [43]. Additionally, along with the established conservative and surgical treatment options, laser assisted surgical debridement, administration of ozone oil or platelet-rich plasma or platelet derived growth factor over the surgical wound have also been explored [44].

Conclusion

Osteonecrosis of jaw, occurs in patient with bone diseases undergoing systemic anti-resorptive therapy (or) anti-angiogenic therapy (or) radiotherapy, makes the disease multifactorial. Both the two conditions (MRONJ and ORN) have relatively similar clinical presentation clearing the fact that a resemblance in clinical presentation does not necessarily denote a similar pathophysiology. Stage 0 of ONJ has gained more attention currently as bone necrosis does not always lead to bone exposure. Stage I, II and III clinical ONJ is

not diagnosed, provided there is loss of soft tissue probidity [12]. The clinical and microscopic findings in ONJ cases suggests the presence of biofilm mediated infectious process that must be prevented and treated and thus conventional management is favoured by many. But, conservative management with a couple of HBO dives and surgical debridement can turn out to be very costly. So, to lower the financial burden and psychological pressure of the patient, persevering directly to a surgical option can help in cases which are suitable. Patients who have been treated with bone-altering agents but with no visible necrotic bone should be considered 'at risk'. Prophylactic dental treatment can reduce the prevalence of ONJ before starting of any treatment with antiresorptive, anti-angiogenic and radiation therapy. Until and unless need for high tumoricidal doses exists, especially in advanced head and neck cancers, ONJ will certainly continue to remain as a clinical challenge demanding satisfactory treatment to improve the quality of life of the patient. Continued clinical studies are required to know the key players in the development, severity, progression and resolution of osteonecrosis of jaw especially in advanced head and neck cancers.

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