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REVIEW PAPER

Bisphosphonate Related Osteonecrosis of the Jaw: An Update

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Abstract
Objectives The aim of this paper is to summarize different diagnostic criteria as well as probable aetiopathogenesis of bisphosphonates related osteonecrosis of the jaw.
Materials and Methods The electronic search of peer-reviewed journals were performed in MEDLINE (PubMed) database in order to find the relevant articles on bisphosphonates related osteonecrosis of the jaw (BP-related ONJ). The search was restricted to English language articles, published from January 2002 to May 2013. On the basis of these articles, probable aetiopathogenesis and different diagnostic criteria of BP-related ONJ were summarized.
Results BP-related ONJ is related to the development of avascular necrosis or dead jaw bones. In recent literature many given hypotheses show the aetiopathogenesis and diagnosis of BP-related ONJ which are interlinked and have multifactorial nature. Their diagnosis revolves around four main diagnostic criteria that differentiate it from other conditions which can delay bone healing.
Conclusions Factors like potency of bisphosphonates, biology of jaw bone, antiangiogenic property of bisphosphonates and soft tissue toxicity in combination with present infection, other drugs, pre-existing pathologies, compromised immune response and dentoalveolar trauma may lead to development of BP-related ONJ.

Keywords Bisphosphonates · Bisphosphonate-related osteonecrosis of the jaws · Bisphosphonate osteonecrosis

Introduction

Bisphosphonates related osteonecrosis of the jaw (BRONJ) is related to the development of avascular osteonecrosis or osteochemonecrosis [1, 2]. In 2002, the Food and Drug Administration (FDA) received first reports related to several patients with cancer, treated with the IV bisphosphonates (BP), who developed osteonecrosis of the jaw. One year later, BRONJ was first described in medical literature by Marx [4]. Between 1858 and 1906, there was an epidemic of osteonecrosis of the jaw named "Phossy Jaw" among workers in match-making factories who inhale fumes of "yellow phosphorus". Marx [4] points out that yellow phosphorous can react in the human body with H_2O, CO_2 and amino acids, such as lysine; as a result it can make formation of BPs (Alendronate and Pamidronate) like compound. Since then, a number of surgical and dental centres have published their experiences with this newly described condition [3]. In 2012 Reid and Cornish [5] reviewed 2408 cases of BRONJ and reported that incidence of BRONJ after administration of IV BPs in cancer patients was 89 % while rest 11 % had only received oral BPs. In contrast to the above report Sharma et al. [6] in 2013 reported that the incidence rate of BRONJ after IV administration of bisphosphonates has been documented from 0 to 28 % and not more than 4 % in cases of oral BPs administration.

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Review

The electronic search of peer-reviewed journals were performed in MEDLINE (PubMed) database in order to find the relevant articles on bisphosphonates related osteonecrosis of the jaw (BRONJ). The search was restricted to English language articles, published from January 2002 to May 2013. Only those articles have been reviewed which are related to aetiopathogenesis and diagnosis of BRONJ. Due to enormous amount of available literature it is impossible to review and cite all the papers; hence we cited literature only when appropriate. The keywords used for search were bisphosphonate-related osteonecrosis of the jaws, aetiopathogenesis of BRONJ and diagnosis of BRONJ.

Aetiopathogenesis of Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ)

Chemically bisphosphonates have three important entity P–C–P backbone, R_1 and R_2 side chain. P–C–P back bone is responsible for the strong affinity of the BPs for binding to hydroxyapatite (HAP) and allows for a number of variations in structure based on substitution in the R_1 and R_2 positions on the carbon atom. The ability of BPs to bind to HAP crystals and to prevent both crystal growth and dissolution was enhanced when the R_1 side chain was a hydroxy group rather than a halogen atom. On the other hand chemically bisphosphonates had two subdivisions which have different mechanisms of action on osteoclasts based on presence or absence of a nitrogen side chain on the pyrophosphate group (R_2 side chain). Nitrogen containing BPs are poorly absorbed by GIT as compared to non-nitrogen containing BPs. Due to this reason nitrogen containing BPs are commonly prepared for IV administration [7–9]. Co-administration of oral BPs and calcium may interfere with absorption of the bisphosphonates. Calcium along with BPs can decrease the effectiveness of BPs, to avoid this interaction calcium is given 30–60 min before or later in the day [10].

Exact pathogenesis of BRONJ is not known till today, but numerous hypotheses that promote and interlink the development of BRONJ are found in literature. Since the last one decade many publications reported on non-nitrogen containing BPs, which are closely related to pyrophosphate are taken up by the osteoclasts and antagonized the cellular energy pathways due to intracellular liberation of methylene that contains toxic analogs of ATP, which probably inhibit ATP-utilizing enzymes and induce osteoclast apoptosis. While nitrogen containing BPs (Zolendronate, Pamidronate, Alendronate, etc.) have a more complex pathway of action where they inhibit the Mevalonate pathway by inhibition of farnesyl pyrophosphate synthetase leads to prenylation of small GTPase signalling proteins that are essential for osteoclast activity and survival [7–9, 11–13]. Due to alteration of Mevalonate pathway complex biochemical changes occur that finally lead to intracellular accumulation of isopentenyl diphosphate (IPP). In monocytes, the accumulated IPP results in activation and proliferation of γ and δ T cells, triggering pro-inflammatory cytokines release and thus causing acute systemic inflammatory reactions [14, 15].

Another most peculiar feature of BP-related ONJ is the exclusive localization of osteonecrosis to the maxillary and mandibular bones [1, 16–18]. A few recent studies have reported that long term BP therapy may induce osteonecrosis in bone of the hips as well as external ear canal that indicates possible systemic phenomenon of BP therapy [19–21]. Mandibular and maxillary bones have two important components like alveolar bone and periodontium [1]. These two structures of the jaw bone show particularly high bone turnover. That is why bones maintain a high remodelling status throughout life either in response to continuous mechanical stress or as a result of tooth movements or loss. In humans, the bone remodelling rate of cortical bone of the jaw (alveolar process) is 10–20 times faster than that of iliac bone [22]. Naturally, bone remodelling is a physiologically coordinated process involving bone formation by osteoblasts and bone resorption by osteoclasts. Imbalance between these two entities may lead to skeletal abnormalities characterized by increase or decrease in bone density. In contrast to other skeleton, jaw bones, especially alveolar process and periodontium have relatively high vascularity, bone turnover and remodelling because of continuous mechanical stress. In response to continuous mechanical force, osteocytes and osteoblasts of the alveolar process activate bone remodelling by stimulating local over expression of various cytokines, which induces maturation of many new osteoclasts from medullary monocytes precursor and recruit them to the bone surface. While periodontium contains human gingival fibroblasts and human periodontal ligament cell that have a role in osteoclastogenesis through the expression of receptor activator of nuclear factor kappa β ligand (RANKL) on their cell surface. Due to increased mechanical stress, there is increased expression of RANKL on human periodontal ligament cell. On the other hand formation of osteoclasts requires interaction between TNF family molecule RANKL and its receptor RANK. At the same time, human gingival fibroblast and human periodontal ligament cells secrete osteoprotegerin that easily bind to RANKL and inhibits osteoclastogenesis. With the advancement of age, jaw bone remodelling will increase along with periodontal disease and elevated systemic bone turnover which is the most important reason for the development of the BRONJ [1, 23, 24]. Muscle segment

box (MSX-1) is co-expressed with RANKL on cranial neural crest cells derived jaws hard and soft tissue progenitor cells. It is basically related to cellular plasticity and proliferation mediating transcription factor which prevents terminal differentiation and stimulates proliferation of progenitor cells. According to Wehrhan et al. [25] suppressed expression level of MSX-1 and RANKL along with elevated levels of Bone Morphogenic Proteins (BMP) is seen in BRONJ tissues. Therefore Msx-1 is the useful assessment tool to predict risk and for appropriate line of treatment.

In 2006, Ardine et al. [26] reported that patients with BRONJ had persistently higher parathyroid hormone (PTH) levels compared to normals and suggested that higher PTH level may involve in the pathogenesis of osteonecrosis of the jaw. While in 2009, Papapetrou [3] reported in some cases of BP related secondary hyperthyroidism that there may be a relatively smaller reduction of bone turnover caused by the BPs because of the antagonistic effect of the high PTH. In those conditions bone turnover is higher than expected that may lead to accumulation of higher concentration of the drugs in the bone microenvironment. This causes localized, relatively increased BPs related production of interleukin-6 as well as other pro-inflammatory cytokines and an inflammatory reaction localized to bones. Recently in 2012 Saavedra et al. [27] reported BPs may produce an asymptomatic decrease of serum calcium and an increase in PTH. According to them the increase in PTH level is due to the effect of antiresorptive therapy and the natural physiological aging process.

Many authors have suggested that BPs causes local impairment of the response to localized bone injury due to decrease in cellularity and blood flow in bone. In BRONJ large number of osteoclasts have been detected close to actively resorbing bone and this accumulation is likely to mimic the healing process while alterations in the intraosseous blood flow have been hypothesized as pathological cause of BRONJ. The effect of these alterations has been named as "drug induced avascular necrosis of the jaw". Hellstein and Marek in 2005 [28] reported intact vascular channels even in areas with acute inflammatory infiltrates and bacterial overgrowth. In their own histological findings of several cases of BRONJ they reported non-vital bone fragments with reduced evidence of osteoclastic action, but no vascular alteration. However, in 2006, Woo et al. [29] reported that blood flow in the mandibular and maxillary bone could be altered by BPs via inhibition of intraosseous angiogenesis on the basis of histological findings. Therefore, antiangiogenic properties of BPs may explain the apparent ischemic changes in BRONJ that was also demonstrated in animal models but only in pathologic tissues (neoplastic or Paget's disease tissue) [1, 29]. Consequently, administration of more potent BPs (N-BPs) in cancer patients have antiangiogenic property that participates in development of BRONJ. On the basis of this evidence Vincenzi et al. [30] evaluated the role of vascular endothelial growth factor (VEGF) as a predictive marker of BRONJ and found decreased VEGF circulating levels at days 7 and 21 after the 1st administration of N-BPs. Thus the authors concluded that the anti angiogenic properties of N-BPs are directly linked with BRONJ pathogenesis and serum VEGF levels can represent an effective early predictive marker.

Jaw bones do not appear to accumulate BPs at a significant higher concentration than the reminder of the skeleton despite its higher turnover [31]. Reid in 2009 [32] reported that BPs cause soft tissue toxicity that might be responsible for the development of BRONJ. According to his publication the exposure to micromolar concentrations of these compounds in solution produces toxic effects in many cells including monocytes, macrophages, periodontal ligament fibroblasts, endothelial cells, variety of tumour cells, osteoblasts and epithelial cells. But it is not clear what types of concentration of BPs on bone surfaces are toxic to adjacent cells. In 2008, a study by Coxon et al. [33] explained the mechanism for BP toxicity on non-osteoclast cells. According to them, in the absence of bone surface, BPs in solution is taken up by cells, resulting in toxicity mediated through its inhibition of the Mevalonate pathway while in presence of bone surface, BPs shows more affinity to hydroxyapatite crystals and was not available for non-bone cells. Thus it proved that BPs cause direct toxic effect on the soft tissues of the oral cavities in vitro, an effect which was increased in low pH environment that is most commonly found in cases of presence of local infection. The uptake of BPs by the skeleton is so efficient that concentrations in human plasma are unmeasurable within a short period of BPs administration and there is no evidence that BPs released from bone during its metabolism, even in the presence of increased resorption associated with low pH, reaches concentrations sufficient to be toxic [31–35].

According to Park et al. [36], BRONJ also developed in those compromised patients who undergo renal transplantation followed by administration of long term oral BP therapy. They also reported that extraction was the main provoking factor for the development of BRONJ. Therefore, adequate dental care is required before and after renal transplantation to reduce the risk of BRONJ.

Diagnostic Criteria

Different diagnostic criteria, such as clinical presentation, radiographic evaluation, histopathological examination and laboratory investigations are very important for the diagnosis of BRONJ. All these are associated with

pathophysiology of BRONJ and play an important role for early detection and management of BRONJ.

Clinical Presentation

BRONJ pathology presents with a clinical and radiographic appearance similar to that of radiation necrosis (osteoradionecrosis) [11]. Many authors reported serious and previously unrecognized oral complications of BPs therapy which may manifest as poor wound healing, spontaneous intraoral soft-tissue breakdown leading to intraoral bone exposure and bone necrosis in the oral and maxillofacial region [24, 37].

Patients may present, during routine dental assessments, as having asymptomatic exposed alveolar bone, without any evidence of erythema or discharge or present with pain and evidence of local infection, or occasionally widespread infection, a discharging sinus or even a pathological fracture of the jaw. There may be a history of invasive dental treatment or local trauma from dental prosthesis, but in some cases there will be no obvious preceding factors [31]. Although, in 2009, the American Association of Oral and Maxillofacial Surgeons (AAOMS) [18, 38] defined BRONJ, as "patients may be considered to have BRONJ if all of the following three characteristics are present: (1) current or previous treatment with a BP, (2) exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws".

According to NSW Health Guideline [18, 39], an additional character was added in AAOMS working definition of BRONJ; there is no evidence of cancer at the site. Lesions in patients who have not fulfilled the above four characteristics should be excluded from the diagnosis of BRONJ [31, 38–42].

Radiological Features

Radiographic findings of BRONJ are not specific and are found in other conditions like osteomyelitis, osteoradionecrosis and metastatic bone lesions also. According to previous publications, most commonly imagined finding in osteonecrosis of the jaws is osseous sclerosis. This can vary from subtle thickening of the lamina dura and alveolar crest to attenuated osteopetrosis like sclerosis. Other findings like osteolysis, soft tissue swelling, periosteal new bone formation, periapical lucencies, oroantral fistula and sequesters are likely to correspond with the presence of infection [22, 43]. It is imagined that differential diagnosis includes chronic sclerosing osteomyelitis, osteoradionecrosis, bone metastasis and Paget's disease. If osteonecrosis is suspected, different imagined techniques may be performed to confirm diagnosis and extent of the lesions [42]:

- Periapical radiograph and cone beam computed tomography (CBCT): reveals generalized thickening of the cortical plate and lamina dura, mixed sclerotic and lytic bone destruction involving alveolar bone and basal bone, sequesters, encroachment on the mandibular canal and maxillary antrum and pathological fracture while thickening of cortical plate in the affected region was the only radiological findings of CBCT [44].
- Computed tomography (CT) images: reveal sclerotic changes, osteolytic changes, periosteal bone proliferation, sequestration and inferior alveolar canal involvement while contrast enhanced magnetic resonance imaging (MRI) reveal intensity changes of the cortical and sub cortical bone structures, contrast enhancement in necrotic bone area, soft tissue involvement and cervical lymphadenopathy [45].
- $^{99}Tc^{m}$-MPD: reveals detection of local bone remodelling activity/high bone turnover sites but presence of increased uptake was confirmed through the single photon emission CT (SPECT) scan because it provides a high degree of accuracy [42].

Histopathologic Features

Histological examination revealed non-vital bone tissues in both BRONJ and IORN but BRONJ tissue revealed diffuse and patchy area of necrosis while IORN tissue showed larger and not diffusely distributed area of necrosis. In the IORN cases numerous osteoclasts could be detected close to vital bone. In 2013 Sharma et al. reported that BRONJ was characterized by presence of osteocyte-depleted bone lacunae which was more commonly seen in the deeper layers of the bone while lacunae located towards the surface of the bone lamellae will lose the osteocytes at a later stage [6, 46]. Recently specimens of BRONJ/IORN tissues show necrotic bone surrounded by many bacterial colonies. Some of these are morphologically compatible with Actinomyces colonies in both the disease conditions. Regarding this Ficarra and Beninati in 2007 reported that special stains such as PAS and Gram staining can be useful to further confirm the findings of Actinomyces in BRONJ while Aas et al. in 2010 reported a semi-nested PCR testing based on 16S r-RNA gene for the presence of Actinomyces species was performed in three cases which confirmed the presence of A. israelii in IORN [47, 48]. Therefore, it was concluded that Actinomyces was involved in the chronic, non-healing inflammatory processes as a characteristic feature of both diseases. Together with the associated presence of increased osteoclast numbers, it was concluded that both factors may be involved in osteolytic mechanism.

While the soft tissue evaluation shows proliferating stratified squamous epithelium with arcading of rete pegs and neutrophilic exocytosis and the adjacent fibrous connective tissue revealed the presence of patches of plasma cells, interspersed neutrophils and surgical haemorrhage that was similar to osteomyelitis [11, 24, 49].

Gram staining may reveal normal oral flora or, in cases of concomitant osteomyelitis, may include bacteria commonly found in osteomyelitis. It has been suggested that BP therapy could induce a condition similar to that seen in osteopetrosis [24].

Immunohistochemistry revealed increased expression of hDB-1,-2,-3, reduced expression of TGFβ1 and increased Galectin-3 expression in cases of BRONJ [50, 51]. Microbial cultures may provide identification of the pathogens causing secondary infections (Actinomyces and other pathogens) that were important for selection of appropriate antibiotics.

Specific Laboratory Investigations

In addition to radiographic imaging, a complete blood count may help assess the state of the patient in terms of possible infection. Cultures of the infected bone tend to yield normal oral flora; however, cultures of draining abscesses may be helpful in tailoring antibiotic treatment.

Assays to monitor markers of bone turnover, such as serum or possibly urine N-telopertide (NTx) and C-telopertide (CTx) level may help in the future diagnosis of BRONJ. NTx and CTx are fragments of collagen that are released during bone remodelling and turnover. Bisphosphonates reduce NTx and CTx levels. Monitoring of the risk of BRONJ development through the various phases of BP therapy may also be possible in the future using serum CTx levels, which are thought to be reliable indicators, although they are subject to some daily variations [31, 52–54].

According to recent literature, angiogenesis suppression may play an important role in development of BRONJ.

Differential Diagnosis

Patients who are at risk of BRONJ or those with established BRONJ may also present with other common clinical conditions not to be confused with BRONJ. These conditions include, but are not limited to, avascular necrosis such as alveolar osteitis, osteomyelitis, osteoradionecrosis, sinusitis, gingivitis, periodontitis, caries, periapical pathology and temporomandibular disorders (Table 1) [11, 24, 40, 55].

Some of these conditions, such as periodontitis and periapical pathology could also contribute to the development of BRONJ in patients at risk. Osteoporosis may resemble BRONJ, presenting with an area of denuded avascular bone. However, osteoporosis can easily be differentiated from BRONJ by its classic radiographic appearance and by the lack of history of BP exposure [24].

Management of Bisphosphonates Related Osteonecrosis of the Jaws (BRONJ)

BRONJ is a challenging complication to treat, both in term of limiting the disease condition and the quality of the life of patients. Nocini [56] reported incidence of BRONJ which was at least ten times higher in patients with malignancies than in those treated for osteoporosis for focal diseases. In compliment to the consequence of BRONJ, there was a major difference in morbidity between patients that received intravenous BPs compared to oral

Table 1 Summary of differential diagnosis of bisphosphonates induced osteonecrosis of the jaws (BRONJ)

Disease	Aetiology	Clinical presentations
BRONJ	Multifactorial such as BPs therapy, high bone turnover, concomitant drugs, infection, dentoalveolar surgery, compromised immune response and others	Poor wound healing, spontaneous or postsurgical soft-tissue breakdown leading to intraoral bone exposure, bone necrosis and osteomyelitis. But in advance stages some additional orofacial finding like intense pain, extensive sequestration of bone and cutaneous draining sinus tracts
Osteoradionecrosis	Radiation therapy	Oral mucolytics, xerostomia, loss of taste, trismus, periodontitis, soft tissue necrosis
Alveolar osteitis	Partial or total loss of blood clot in extraction site	Exposed extraction site, pain that may radiate to adjacent structures
Gingivitis	Soft tissue inflammation in response to plaque, bacteria, biofilm	Gingival inflammation (red, swollen, rounded margin, bleeding on manipulation)
Periodontitis	Loss of attachment as a host modulated immune response to plaque, bacteria, biofilm	Gingival inflammation, foul odour, evidence of alveolar bone loss
Periapical pathology	Pulpal necrosis (caries, trauma)	Possible gingival inflammation, gingival sinus tract as well as evidence of periapical lesion

BPs bisphosphonates

BPs. Majority of patients treated with IV BPs show permanent disability while those patients who received oral BPs had frequently healed from the complication [56, 57].

Optimum management strategies of BRONJ is mostly palliative and empirical (to eliminate clinical symptoms like pain, infection and minimize the progression of bone necrosis) before microbial culture report [44, 58]. Later, most authors agreed to the management of BRONJ, started after advised morning fasting serum C-terminal telopeptide (CTx) test and serum VEGF levels, because they are useful assessment tools to predict risk and to make appropriate line of treatment and begin palliative care to restrict the further progression of the disease [52, 59].

A diversity of treatment modalities has been reported in previous literature for oral and IV BRONJ, all offering variable clinical outcomes [60]. Treatments such as 0.12 % chlorhexidine gluconate mouth rinse (if exposed bone is painless), systemic antibiotics (if patient complains of pain and/or clinical evidence of infection) [56, 57] conservative surgical debridement with or without primary flap closure as well as marginal or segmental resection [61] and HBO therapy [62–64] have been used. Some of these treatments are effective in patients while others are not effective and may even worsen their condition. According to previous literature, conservative treatment is the first choice because there is a possibility that dentoalveolar surgery makes the surgical site re-necrotized, and hence should be delayed as long as possible.

Engroff and Kim [65] in 2007 reported two cases of microvascular reconstruction of the mandible in BRONJ patients and found early recurrence in one patient. While in 2008, Nocini et al. [56] reported that mandibular reconstruction with the fibula flap appeared to be appropriate in BRONJ resected patients and does not seem to influence the natural course of the primary disease. Another interesting finding in surgical management of BRONJ is transplantation of intralesional autologous bone marrow stem cell which shows complete response to the lesion [62].

In 2010, Epstein et al. [66] reported that administration of pentoxifylline with α-tocopherol reduces 74 % area of bony exposure and symptom control. While Lau and Adachi [57] reported that, administration of Teriparatide therapy (20 μg sc daily) for 3 months causes significant reduction in the size and number of ulcerations of the mandibular alveolus and noted that a significant increase in the bone regeneration of the extraction socket was seen on panoramic radiography. After 10 months of therapy complete healing of extraction sites was seen along with normal appearing oral mucosa [12]. Recently Cicciu et al. [67] investigated the clinical effect of recombinant human bone morphogenic protein type-2 (rhBMP-2) alone in those BRONJ patients who underwent surgery for necrotic bone removal and found uneventful healing of the necrotic area.

AAOMS position paper that advocated discontinuation of IV BPs therapy shows no short term benefit while long term discontinuation of IV BPs may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development as well as decrease of clinical symptoms. Consequently, discontinuation of oral BPs therapy may lead to gradual improvement in clinical symptoms. Six to twelve months discontinuation of oral BPs may result in either spontaneous sequestration or resolution following debridement surgery.

Conclusions

In the past one decade numerous hypotheses in literature are available that promote and interlinke the development of BRONJ. Factors like potency of bisphosphonates, biology of jaw bone, antiangiogenic property of bisphosphonates and soft tissue toxicity in combination with present infection, other drugs, pre-existing pathologies, compromised immune response and dentoalveolar trauma may lead to development of BRONJ [1, 23, 31, 32]. Exact diagnostic criteria to distinguish BRONJ from other delayed healing conditions are not known as yet. According to the recent literature patients may be considered to have BRONJ if all of the following four characteristics are present: current or previous treatment with BPs, exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, no history of radiation therapy to the jaws and no evidence of cancer at the site. Lesions in patients who have not fulfilled above four characteristics, should be excluded from the diagnosis of BRONJ [38–40, 53, 68]. Incidence of BRONJ was 0.8–12 % [38, 39] in IV BPs and 0.01–0.04 % [38] in oral BPs administration. The clinical presentation, radiographic evaluation, histopathological examination and laboratory investigations are very important for the early diagnosis and management of BRONJ.

BRONJ is a multifactorial disease. It commonly develops in patients who receive either long term nitrogen containing IV BPs therapy alone or associated with invasive dental procedure. Serum VEGF levels and morning fasting CTx levels are useful assessment tools to predict risk and to make appropriate line of diagnosis and treatment. In cases of established disease, management strategies are mostly palliative and empirical.

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