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REVIEW ARTICLE

Periodontal infection in cancer patients treated with high-dose chemotherapy

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Abstract The infected and inflamed periodontium can act as a focus for systemic infection in neutropenic cancer patients. The incidence of these oral infections is unknown, but probably underestimated. Periodontal infections can easily be overlooked, primarily because symptoms of gingival inflammation may be minimal and the infection may be located in deeper parts of the periodontium. Assessment of a patient's periodontal condition before the onset of profound neutropenia is critical to the diagnosis and the management of these potentially life-threatening infections. This review article is aimed at informing supportive care providers of recent insights into the pathogenesis of periodontal diseases and the role of subgingival microorganisms, with the emphasis on these infections in cancer patients treated with high-dose chemotherapy. Furthermore, a multidisciplinary approach to the management of periodontal infections and the need for future research is discussed.

Keywords Periodontal infection · Subgingival microflora · Febrile neutropenia · Oral care

Introduction

Oral and systemic infections emerging from the oral cavity are significant problems in cancer patients treated with intensive chemotherapy regimens, including hematopoietic stem cell transplant (HSCT) procedures [19]. During profound neutropenia patients are particularly at risk of developing infections caused by oral bacteria, but fungi and viruses may also play a part. A substantial number of these infections are associated with oral mucositis, which is the result of complex interaction between the toxicity of cancer chemotherapy to oral mucosal tissues, myelosuppression, and the oral microflora [48].

In addition to infections arising from ulcerated oral membranes (e.g. mucositis), there is evidence that preexisting infections around the teeth (periodontal infections, e.g. gingivitis and periodontitis) are associated with fever and sepsis in these patients [15, 30, 34, 36, 44].

Ulcerated periodontal pocket epithelium can act as a portal of entry for translocation of microorganisms into the bloodstream [51]. In addition, inflamed and infected periodontal tissues may serve as a reservoir of endotoxin (lipopolysaccharide, LPS), pro-inflammatory cytokines, and other inflammatory mediators which may spread systemically [28].

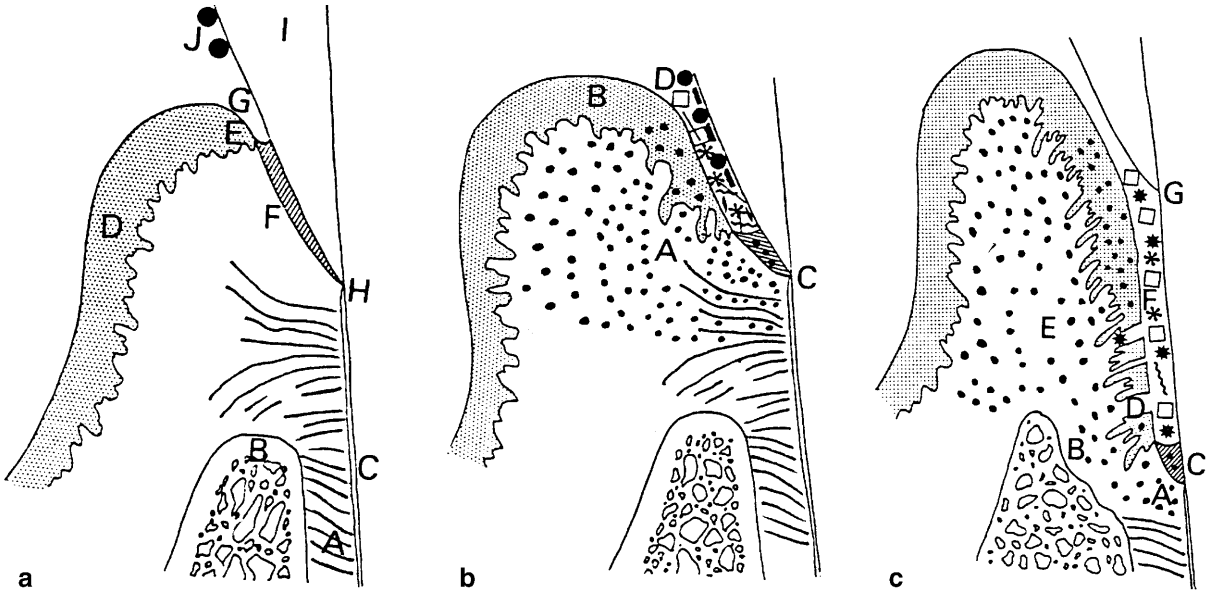

Fig. 1 a Healthy periodontium (*A* periodontal ligament, *B* alveolar bone, *C* cementum, *D* oral epithelium, *E* sulcular epithelium, *F* junctional epithelium, *G* gingival sulcus, *H* cement–enamel junction, *I* tooth enamel, *J* supragingival dental plaque microflora). b Established gingivitis lesion (*A* inflammatory cell infiltrates in gingival connective tissue, sulcular epithelium, and junctional epithelium, *B* gingival tissue swelling leading to increased gingival sulcus depth, *C* junctional epithelium at cementum enamel junction, *D* subgingival dental plaque microflora). c. Periodontitis lesion (*A* loss of connective tissue attachment, *B* loss of crestal alveolar bone, *C* apical migration of junctional epithelium, *D* ulceration of periodontal pocket epithelium, *E* inflammatory cell infiltrates in gingival connective tissues, sulcular epithelium, and junctional epithelium, *F* deepened periodontal pocket and pathogenic subgingival microbial flora, *G* cement–enamel junction). Adapted with permission from [46]

Particularly in neutropenic cancer patients, periodontal infections can be easily overlooked or misdiagnosed, and thus their contribution to fever, bacteremia, and sepsis may be underestimated. Gingival infections can be missed because symptoms of gingival inflammation, such as redness and swelling, may be muted as a result of the lack of neutrophils. On the other hand, periodontal infections may be associated with marked gingival redness, tenderness and pain during neutropenia. Nevertheless, if such an exacerbation of gingivitis and/or periodontitis coincides with severe oral mucositis, the condition may be overlooked or incorrectly ascribed to mucositis. Furthermore, and probably most importantly, in patients with severe periodontitis the infection affects the deeper parts of the periodontium, and it should be realized that such an infection cannot be diagnosed by visual inspection.

An infectious cause is suspected but never confirmed in up to 40% of episodes of neutropenic fever [8]. It is feasible, however, that some proportion of these febrile episodes can be attributed to unrecognized periodontal infections. There is also circumstantial evidence suggesting that subgingival microorganisms and cytokines from pathologic pockets translocate into the oral cavity and may contribute to oral mucositis [5] and to lower respiratory tract infection [18, 42, 43].

Given that periodontal infections in cancer patients may cause significant morbidity and are potentially life-threatening, the present paper aims to inform supportive care providers about recent insights into the etiology and the pathogenesis of periodontal diseases. In addition, the literature on periodontal infections and their potential systemic sequelae in neutropenic cancer patients will be reviewed and recommendations for prevention, management and future research will be provided.

The periodontium and periodontal diseases

The tissues that support the dentition form the periodontium. These include the root cementum, the alveolar bone, the periodontal ligament that connects the teeth to the jaw, the gingiva and the alveolar mucosa (Fig. 1a). The gingiva, which can be divided into the free gingiva and the attached gingiva, is the only site of the body where the continuity of the epithelial protective lining is interrupted. One of its roles is to protect the underlying periodontal tissues against microbial invasion. In periodontally and otherwise healthy adults it is estimated that 530,000 leukocytes (predominantly neutrophils) migrate every minute from the small vessels of the subgingival plexus through the junctional epithelium into the oral cavity [37]. The protective properties of the gingival epithelium are often compromised by oral microorganisms present in dental plaque, which is a biofilm that adheres to the tooth surface at or below the gingival margin. Ma-

ture dental plaque contains up to $1–2\times10^{11}$ bacteria per gram, a similar bacterial density to that in the colon. In the majority of people, the continual presence of subgingival dental plaque results in inflammation of the gingiva (gingivitis, Fig. 1b). Chronic marginal gingivitis is characterized by red swollen gums which bleed easily, and by the production of gingival crevicular fluid (GCF), a serum transudate. The microflora of the subgingival plaque associated with gingivitis is predominantly composed of Gram-positive organisms (*Streptococcus* spp., *Actinomyces* spp., *Peptostreptococcus micros*), but also includes Gram-negative bacteria (such as *Fusobacterium nucleatum* and *Prevotella intermedia*).

In a susceptible individual, subgingival colonization of putative periodontal pathogens may lead to the development of periodontitis. This is a chronic inflammatory disease, affecting the deeper parts of the periodontium. As dental plaque migrates subgingivally in the apical direction, the periodontal attachment apparatus is degraded, leading to the formation of periodontal pockets and to reduced tooth support (Fig. 1c). Periodontitis usually progresses slowly, and although a considerable amount of ulcerated pocket epithelium may be present (up to 35 cm^2 in severe, untreated periodontitis) it is seldom painful. Although over 350 bacterial species have been isolated from dental plaque, it is well documented that the progression of periodontitis is associated with a limited number of pathogenic Gram-negative obligately or facultatively anaerobic bacteria, including *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Actinobacillus actinomycetemcomitans*, *Treponema* spp., and *Fusobacterium nucleatum*. In patients with periodontitis, subgingival plaque may also harbor enteric bacilli, coagulase-negative staphylococci, *Pseudomonas* spp. and *Candida albicans* [7, 45, 47], which can potentially contribute to the destruction of connective tissues and bone.

A wide variety of host–parasite interactions take place in the gingival tissues (reviewed in [31]). Briefly, bacterial substances, such as LPS, activate resident tissue macrophages to produce interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), matrix metalloproteinases (MMPs), and prostaglandin E_2 (PGE_2). Vascular permeability and the expression of adhesion molecules increase, resulting in enhanced migration of leukocytes, edema, and the formation of an inflammation infiltrate consisting of macrophages, emigrating neutrophils, lymphocytes (including T cells of both helper-1 and T helper-2 phenotypes and B cells), and plasma cells. If the infection persists, subsequent tissue destruction may occur possibly as a result of continual B cell activation and unregulated production or large amounts of IL-1.

Risk factors have been identified that are associated with the development and progression of chronic periodontitis. These include poor oral hygiene, smoking, psychological stress, systemic diseases, increasing age, and heredity. A number of studies have focused on genetic traits involved in immune responses that may confer enhanced susceptibility to periodontitis. Data indicate that two polymorphisms in the cluster of genes encoding for IL-1, when found together, are associated with increased severity of periodontitis, and probably also with increased susceptibility to this disease [20]. One of these variants in the *IL-B* gene has been associated with a 2- to 4-fold increase in IL-β production.

In addition to chronic periodontal diseases, acute forms of periodontal diseases occur. Acute necrotizing ulcerative gingivitis (abbreviated to ANUG in the American literature and to NG in the European literature) is an acute infection of the gingiva characterized by interdental soft tissue necrosis, ulceration and bleeding. The gingival connective tissues are invaded by spirochetes and there is a predominance of *Prevotella intermedia* and *Fusobacterium nucleatum* in the subgingival microflora. Necrotizing gingivitis is associated with underlying impaired immune responses, and it may be one of the first oral signs of acute leukemia or HIV infection [27]. If the infection results in the loss of periodontal attachment and the destruction of bone, it is called necrotizing periodontitis, or necrotizing stomatitis if progression extends beyond the mucogingival junction and into the adjacent mucosa and bone. Infections of the periodontium may also be associated with other bacteria (e.g. streptococci and *Pseudomonas* spp.), fungi (*Candida* spp. and *Aspergillus*) or with herpesviruses [6, 12].

Periodontitis as a putative risk factor for systemic conditions

The subgingival biofilm may exert greater influence than the adjacent periodontal tissues [29, 49]. Recent epidemiological studies suggest an association between poor oral health, including periodontitis and systemic conditions (e.g. respiratory diseases [18, 42, 43], diabetes mellitus [16], coronary heart disease and stroke [3], and adverse pregnancy outcomes [28]). This has led to new investigations carefully designed to further explore whether periodontitis is an independent risk factor for these conditions and to a surge of research aimed at elucidating underlying biological mechanisms. There is evidence suggesting that subgingival bacteria, microbial components, TNF-α, IL-1 and other inflammatory mediators can spread into the salivary secretions and into the systemic circulation and may compromise general health. Patients with untreated, severe periodontitis have transient bacteremia following chewing and oral hygiene procedures [51]; periodontal pathogens have been identified in atherosclerotic plaques [17] and may invade fetal tissues [29]. Recent studies suggest that periodontal infection induces a mild acute phase response (APR) in the liver, since activators of the APR, such as IL-6, and APR

proteins, such as C-reactive protein (CRP) and haptoglobin, were found the be increased in the serum of patients with periodontitis [9, 14, 23].

Periodontal infections in neutropenic cancer patients

There are numerous reports on oral infections in myelosuppressed cancer patients (reviewed in [25]). However, few of these studies focus on infections of the periodontium. There is evidence to show that pre-existing periodontal infections (gingivitis as well as periodontitis) may induce fever and that microorganisms may spread systemically [15, 21, 30, 33, 34]. It can be speculated that the risk of developing systemic infection is associated with the severity of periodontal disease (e.g. the total surface area of ulcerated pocket epithelium) and the composition of the subgingival microflora. Nevertheless, at present the relative contribution of gingivitis and periodontitis to systemic infection in neutropenic cancer patients is largely unknown. Figures on the incidence of so-called acute periodontal infections reported in studies performed in the 1980s show significant disparity [30, 32, 34, 35, 36, 39]. Initially, 28% of all clinically defined infections in 22 leukemia patients who developed neutropenic fever during remission-induction therapy were reported to be periodontal [30]. A high incidence of acute periodontal infections was also reported in patients with other malignancies [35]. In subsequent investigations, however, acute periodontal infections either did not develop at all [36, 39], or only very infrequently [50]. Nearly all patients in these studies had pre-existing chronic periodontal infections, ranging from mild gingivitis to severe periodontitis. These inconsistencies may be explained at least in part by the mode by which acute periodontal infections were defined and subsequently diagnosed, namely by the presence of gingival tenderness on palpation in a febrile patient (core temperature ≥ 38.3°C). Although localized gingival and periodontal abscesses accompanied by distinct or only minimal signs and symptoms of acute inflammation (including tenderness) may develop in neutropenic cancer patients, tenderness seems an inaccurate marker by which to assess all periodontal infections that may give rise to systemic infection. Systemic infection induced by generalized “asymptomatic” chronic infections localized deep in the periodontal tissues may have been especially underestimated. Moreover, it can be speculated that measures to improve oral hygiene during hospitalization or advances in antiviral therapy have contributed to a reduction of gingival or periodontal abscesses.

Another approach to the study of a possible contribution of periodontal infections to fever was utilized by Laine et al. [21], who reported that patients who were treated with chemotherapy for lymphoma and also had severe periodontitis experienced more febrile episodes than did those with a healthy periodontium. Greenberg et al. [15] demonstrated in a prospective study directed at determining the incidence of bacteremia originating from subgingival and other oral sites that the microorganisms isolated from peripheral blood (mainly *Klebsiella* spp.) during febrile neutropenia were similar in terms of their biotypes to those cultured from subgingival plaque of periodontally diseased teeth. These microorganisms could not be isolated from other routinely cultured body sites, nor did physical examination reveal other sites of infection. Interestingly, no distinct gingival signs and symptoms of acute inflammation were observed in patients suffering from severe periodontal disease.

Other studies also analyzed the subgingival microflora before and during intensive chemotherapy. More strictly anaerobic black-pigmented Gram-negative rods were recovered from periodontally diseased sites in cancer patients than in patients with a similar degree of periodontal disease but no cancer [35]. Minah et al. [26] found proportional increases of *Klebsiella pneumonia* and *Pseudomonas* spp. in more than 50% of myelosuppressed cancer patients with advanced periodontitis. Increased proportions of subgingival enteric bacilli, staphylococci, and *Candida albicans* were reported by Reynolds et al. [39] following 14 days of high-dose chemotherapy.

Intensive chemotherapeutic regimens facilitate colonization of subepithelial gingival tissues and bacterial invasion, as shown by Sanavi et al. [41] in an animal model. Light and electron microcroscopy revealed severe loss of sulcular and junctional epithelial integrity around ligated molars (experimentally induced periodontitis) of rats receiving cyclophosphamide. Neutrophils were absent in the junctional epithelium, and bacteria (mainly Gram-negative bacilli) were shown to penetrate deep into the periodontal tissues.

The periodontium may have served as an unidentified source and portal of entry in case reports of life-threatening systemic invasion by the Gram-negative bacteria *Capnocytophaga* and *Fusobacterium nucleatum* in neutropenic cancer patients [2, 4, 22].

Nowadays, the overall incidence of bacteremia caused by Gram-negative bacilli in neutropenic patients is relatively low, since most cases of bacteremia result from Gram-positive bacteria. It is likely that supportive care regimens, including antibacterial prophylaxis, oral care measures, protective isolation, and precautions in food preparation, have contributed to this shift. Nevertheless, the efficacy of these measurements in affecting the subgingival flora in severely periodontally diseased pockets is questionable, and thus a deep periodontal pocket may act as a reservoir for a wide variety of microorganisms, including Gram-negative aerobes and anaerobes, Gram-positive bacilli, viruses, and fungi.

Moreover, it is possible that a cascade of systemic inflammatory responses can be induced without the infecting organism itself actually disseminating into the blood-

stream [52]. It can be speculated that bacterial substances (such as LPS) and pro-inflammatory cytokines present in inflamed and infected periodontal lesions are capable of inducing such a response.

Prevention and management

Oral evaluation, including an assessment of the level of oral hygiene and of the periodontal condition, should be performed early in the work-up for any patient in whom profound and prolonged neutropenia is anticipated (high-risk patients). Gingivitis is assessed by measuring gingival redness, swelling, and bleeding. It should be taken into consideration that in patients with hematological malignancies the hematological status may be reflected in the gingival tissues. For instance, the oral mucosa, including the gingiva, may look pale as a result of anemia, and inflamed gingiva may bleed extensively as a result of thrombocytopenia. In addition, leukemic cells may have infiltrated the gingiva in patients with acute myeloid leukemia. Periodontitis is diagnosed by measuring pocket depths and loss of attachment by means of a periodontal probe supplemented by radiographs. Although there have been no large studies on the risk/benefit or the cost/benefit ratio, there is evidence that periodontal treatment is beneficial if performed prior to the initiation of high-dose chemotherapeutic regimens [5, 15, 32]. Periodontal therapy consists of a number of measures aimed at reducing gingival inflammation and pocket depths. Physical disruption and removal of the biofilm by means of scaling and root-planing, together with instruction on oral hygiene measures to prevent recolonization, are an essential component of periodontal infection control. In selected cases the additional use of antiseptics and local or systemic antibiotics is indicated. Depending on the white blood cell and platelet counts, it should be decided whether prophylactic antibiotics or platelet transfusion are required when invasive procedures are performed [1]. It is beyond the scope of this article to review pretreatment dental strategies in detail, but it is crucial that the oral bacterial load is reduced as much as possible. It should be realized that (unless rigorous extractions are performed) complete elimination of pre-existing periodontitis prior to the initiation of chemotherapy is an unrealistic goal. The medical and the nursing staff should be informed of the patient's oral condition.

During chemotherapy good oral hygiene should be continually maintained to prevent the accumulation of dental plaque [11, 13, 38]. Chlorhexidine is indicated if tooth brushing and the removal of interdental plaque are difficult. Ideally, the oral cavity should be inspected regularly by a dental professional to identify oral complications at an early stage, and to coordinate oral care. During neutropenia, periodontal probing and other procedures to diagnose periodontitis should be avoided, which means that pretreatment evaluation is critical. Moderate to severe periodontitis present in a patient who develops neutropenic fever should be considered as a clinically defined infection, even if gingival signs and symptoms of inflammation are not observed. In high-risk patients this is an indication for the addition of antimicrobial agents against anaerobic bacteria (e.g., metronidazole) to the empirical antibiotic regimen. In such patients culturing of samples from periodontally diseased pockets can provide information pertinent to infection management, since in addition to anaerobic or facultative periodontal pathogens these pockets may harbor Gram-negative aerobic bacteria, Gram-positive bacteria (e.g. coagulase-negative staphylococci) and fungi. Comparison of these results and those obtained from blood cultures will indicate whether bacteremia has originated from the periodontium. If this is the case, further periodontal sampling may be helpful to ensure effective eradication of the offending pathogen.

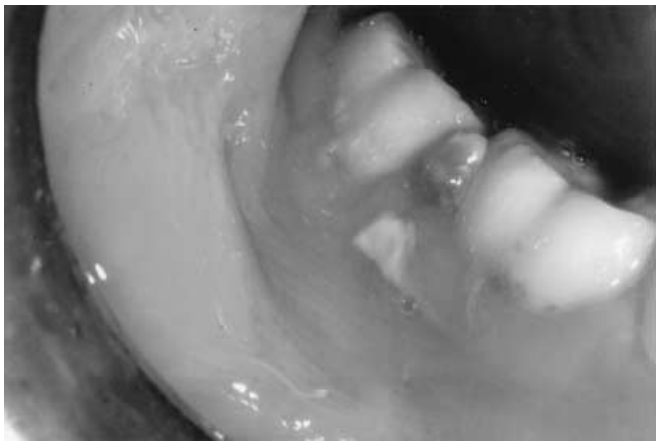

Fig. 2 Gingival infection with clear signs and symptoms of inflammation following hematopoietic stem cell transplantation. This lesion was cultured positively for herpes simplex virus, although bacteria may have contributed to infection. However, it should be well appreciated that periodontal infections may induce fever, bacteremia and sepsis without notable signs of localized inflammation

Gingival and periodontal infections with clearly visible gingival inflammation also represent putative origins of systemic infection. In addition to bacterial and fungal infections, gingival lesions may be initiated by reactivation of viral infection. Clinical findings that suggest viral involvement include rounded 1- to 2-mm ulcerations which coalesce into larger lesions (Fig. 2). The diagnosis is supported by direct virus detections in exfoliated cells or by viral culture [10].

The intervals between chemotherapy cycles may provide a good opportunity for improving oral and periodontal health.

Diagnosis and management of the periodontium in patients undergoing HSCT basically involve applying the principles of good oral care to those being treated with intensive chemotherapy alone [24, 40]. Oral complications depend on the conditioning regimen (e.g., total-body irradiation) and the nature of the transplant (autologous versus allogeneic). Reduced salivary flow increases the risk of oral infection. There is also anecdotal evidence suggesting that meticulous oral hygiene measures and good periodontal health care are important for controlling graft-versus-host disease [24].

Recommendations for future research and concluding remarks

More studies are needed to obtain information on the contribution of periodontal infections to fever, bacteremia, and sepsis in neutropenic cancer patients. These investigations should be directed at both chronic and acute forms of gingivitis and periodontitis and should be performed in larger numbers of patients. In addition, it is important to control for variables such as age, the severity of pre-existing periodontal disease, other oral infections, level of oral care, type of malignancy, cancer treatment, antimicrobial agents and other non-oral clinically or microbiologically defined infections. More information should be obtained on the subgingival microbiota during profound neutropenia and the efficacy of preventive antimicrobial regimens (which differ considerably between cancer centers) to eliminate Gram-negative aerobic bacilli and fungi from periodontal pockets. Moreover, it has been suggested that anaerobic oral bacteria are likely to be selected for by quinolones, such as ciprofloxacin, to which many of these bacteria are only marginally susceptible or not at all [8]. When culturing anaerobic bacteria, the fastidious nature of these microorganisms should be taken into consideration, as this may complicate their recovery from oral samples and blood [51].

Another challenge is to document whether fever and sepsis may have been induced by substances from periodontal bacteria or inflammatory mediators that have entered the circulation. Of interest is the suggestion from Offenbacher [28] that any systemic challenge with LPS or TNF-α may alter the permeability of the gut. Thus, it is possible that periodontal LPS and cytokines may contribute to the additional release of enteric LPS into the bloodstream. This can best be investigated in appropriate animal models. The possibility that patients with specific genetic markers associated with increased IL-1 production and periodontitis susceptibility may also be more disposed to develop sepsis as a result of an exaggerated host-innate inflammatory response that is simultaneously a risk factor for both periodontitis and systemic inflammation is another intriguing subject for future investigation [29]. In this case, periodontitis may serve as a marker of this underlying inflammatory trait. These patients may also develop more severe oral and gastrointestinal mucositis. A further question that needs to be addressed is whether periodontitis is an additional risk factor in lung infections during neutropenia, since supra- and subgingival bacteria, periodontal disease-associated enzymes and cytokines shed into the saliva may induce or facilitate the development of these infections [42, 43]. Periodontitis may contribute to the severity of mucositis by similar mechanisms.

Cancer rises in frequency with age, and advanced age is no longer an exclusion criterion for intensive chemotherapy. Since the prevalence of periodontitis also increases with age, it can be anticipated that more patients suffering from this condition will receive cancer chemotherapy than in the past.

Taken together, there is a clear need for close multidisciplinary co-operation between dental professionals, oncologists, hematologists, specialists in infectious diseases, and other supportive care providers to expand our knowledge of periodontal infections in neutropenic cancer patients, and to improve strategies for prevention and treatment of complications.

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