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Review

Periodontal disease and periodontal management in patients with cancer

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Abstract

Periodontal infection may exacerbate during cancer therapy and may result in oral pain and infection, and systemic infection, which may cause morbidity and can lead to mortality in neutropenic cancer patients. Periodontal disease in head and neck cancer patients treated with radiation therapy may lead to acute and chronic complications. The literature was reviewed by a search of Medline of the National Library of Medicine. The search was conducted to identify publications assessing periodontal disease in cancer patients. In addition, a review of papers referenced in the retrieved papers was conducted to identify additional publications for review. Periodontal disease should be assessed and managed prior to medical treatment of cancer for those with oropharyngeal cancer, and for patients in whom neutropenia may develop during treatment. Pretreatment assessment and management, and maintenance of oral hygiene have been shown to be effective in preventing oral and systemic complications during treatment. A complete oral and periodontal examination is appropriate for all patients planned to receive head and neck radiation therapy and those to be treated with medical protocols that are anticipated to result in neutropenia. Oral and periodontal care must continue following cancer therapy, and requires that the health care provider have an understanding of the malignant disease, oral manifestations of the disease, medical management of the disease, and of the oral complications that may develop.

Keywords: Periodontal disease; Periodontal management; Cancer

1. Introduction

Malignant diseases may present with gingival and periodontal involvement. Squamous cell carcinoma (SCC) of the gingival and periodontal tissues is uncommon. Other malignancies, such as those of the hematopoietic system, may present with periodontal involvement prior to and following the diagnosis of the systemic disease. Metastatic lesions rarely affect the gingival tissues. In addition to manifestations of the malignant disease, pre-existing periodontal disease may affect the outcome of therapy. Therefore, evaluation of the periodontal status is necessary prior to management of head and neck malignant disease, management with high dose chemotherapy prior hematopoietic cell transplantation (HCT) and where the treatment will result in myelosuppression. During medical therapy, pre-existing periodontal conditions may exacerbate resulting in local and systemic complications. Furthermore, the management of malignant disease may have a significant effect upon dental treatment options following therapy and knowledge of the prior treatment is needed. The health care provider must be aware of both the oral and dental implications of the malignant disease and medical therapy in order to select the most appropriate preventive and therapeutic management for the patient.

2. Patients with head and neck cancer

Radiation therapy that involves the oral cavity and salivary glands in the treatment volume may have dramatic effects upon oral health, resulting in the need to

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prevent and treat acute and chronic conditions prior to and during therapy, as well as in continuing treatment considerations for the life-span of the patient. The acute effects of radiation therapy include mucositis, altered salivary gland function, and the risk of mucosal infection. The long-term effects are due to changes in vascularity and cellularity of soft tissue and bone, salivary gland damage, and increased collagen synthesis resulting in fibrosis. These changes result in hypovascular, hypocellular, and hypoxic tissue [1–4]. The affected bone and soft tissue have a reduced capacity to remodel and may be at increased risk of infection and necrosis.

The periodontium is sensitive to the effects of radiation at high doses [1–11]. Blood vessels in the periodontium, periosteum and the periodontal ligament [1,3,7,8] may be affected leading to widening of the periodontal ligament space [9–11]. These changes may result in increased risk of periodontal disease, and impaired capacity of bone remodeling and repair [1,12,13] and rampant periodontal destruction may occur in the absence of good oral hygiene [12]. The degree of compromise of the periodontium may be further affected by occlusal trauma. Prediction of long-term tooth stability is also impacted by root form and an adverse crown to root ratios. Because of these effects, the periodontal status of teeth to be included in the high dose radiation fields must be assessed prior to radiation therapy and teeth that cannot be reliably maintained for a lifetime may require extraction prior to irradiation [14,15]. It has been shown that pre-radiation extraction of teeth carries a lower risk of osteonecrosis than teeth extracted following radiation therapy [16].

Periodontal involvement of teeth in high dose radiated sites can lead to the development of osteonecrosis [17]. Increased tooth loss and periodontal attachment loss in teeth remaining in high dose radiated fields has been documented [18]. It is important to recognize that attachment loss is greater in teeth in irradiated sites, and therefore, pre-radiation treatment planning should include consideration of the impact of additional attachment loss over time that may impact remaining teeth [18]. The increased periodontal involvement and loss of teeth in the high dose fraction indicates a local radiation effect on the tissue, likely due to changes in cellularity, vascularity, and reduced healing/remodeling potential of the periodontium. Decreased saliva volume has been shown in patients with Sjogren's syndrome to result in increased risk of alveolar bone loss, attachment loss, and increased cemento-enamel junction-alveolar bone crest distance [19]. In patients with head and neck cancer, the periodontal breakdown in xerostomic patients appear comparable to reports in patients with Sjogren's syndrome, although more significant periodontal destruction occurs in teeth within irradiated bone [18].

A UK study found that only 11.2% of patients who reported regular attendance at general dentists prior to a diagnosis of oral cancer were considered to have no dental conditions that required treatment before radiation therapy [20]. The dental and periodontal status in a patient planned to receive radiation therapy is assessed by criteria that differ from those used to assess the other patients. This difference may precipitate a recommendation to extract teeth that might otherwise remain under observation in non-cancer patients. The provider must be knowledgeable and understand the basis of radiation therapy, the planned radiation treatment for each patient (radiation dose, schedule, and fields) and the oral/dental/periodontal status in order to develop the best pre-radiation dental treatment plan (Table 1) [22]. Teeth in the high dose radiation field that should be extracted prior to radiation therapy are those that are non-restorable, or that require significant restorative, periodontal, endodontic or orthodontic intervention and

Table 1

Pre-radiation treatment oral assessment
Definitive diagnosis
Medical history
Dental history/past dental care/dental hygiene status
Complete dental exam (mucosal dental exam, periodontal. TMJ)
Radiographic survey (panoramic and adjunctive periapicals or full-mouth periapicals)
Saliva tests (unstimulated and stimulated saliva volumes)
Adjunctive tests as indicated (e.g. pulp tests, cultures)
Prognosis for cure vs. palliation
Proposed treatment (radiation dose/No. fractions)/date of treatment and radiation fields/chemotherapy
Pre-chemotherapy treatment oral assessment
Definitive diagnosis
Medical history, systemic status (CBC, etc.)
Dental history/past dental care/dental hygiene status
Dental exam (mucosa, dental exam, periodontal, with focus on sites of symptomatic infection)
Adjunctive tests as indicated (e.g. pulp tests, cultures)
Prognosis for cure vs. palliation
Planned treatment/date of treatment

those with moderate to severe periodontal disease (pockets of $\geqslant 5$ mm, and those with advanced recession with or without mucogingival involvement; Table 2). In patients with limited past dental care, poor oral hygiene and evidence of past dental/periodontal disease more aggressive pre-radiation dental management should be considered. Additional factors that may modify the recommendation for pre-treatment extractions include the position of the teeth that may be extracted, and the relative importance of individual teeth for future restoration and function, such as teeth that may serve as abutments for prosthesis. Other factors that should be considered, particularly in multi-rooted teeth, include difficulty in oral hygiene, taurodontism, root anatomy (short, tapered, narrow roots), position and orientation of the tooth.

Following radiation therapy compliance with recommendations for oral care is improved with regular post-treatment dental visits for reinforcement of oral protocols [21]. In order to provide dental treatment following radiation therapy knowledge of fields of irradiation is essential. It has been shown that that treatment including periodontal surgery is possible if necessary even within prior radiated sites, which may be more easily tolerated than extraction [23].

3. Patients receiving high dose chemotherapy and hematopoietic cell transplant

Periodontal involvement in patients with leukemia may be an early manifestation of disease or may develop during medical therapy. Patients may present with gingival bleeding in those with significant platelet dysfunction. In some patients, more commonly in patients with monocytic and myelomonocytic leukemia, gingival infiltration with leukemic cells may result in gingival hyperplasia. In patients with neutrophil dysfunction or neutropenia, the inflammatory response may be limited or absent, leading to non-healing soft tissue lesions, and poor response to tissue therapy following dental procedures. The reduced inflammatory response may result in few signs and symptoms associated with sites of infection and tissue damage. In cases with reduced red cells the oral tissues may appear pale. The presentation prior to diagnosis and during treatment may be variable, ranging from significant oral changes that may lead to diagnosis of leukemia to minimal findings that are not suggestive of an underlying disease.

Table 2
Consideration for Pre-radiation extractions of teeth in the high dose radiation fraction [31]

Caries–non-restorable
Active periapical disease — symptomatic teeth
Moderate to advanced periodontal disease
Lack of opposing teeth, compromised hygiene
Partial impaction or incomplete eruption of teeth
Extensive periapical lesions (not if chronic or well localized)

The primary focus in management of leukemic patients and those in whom myelosuppression is anticipated treatment of pre-existing infection and prevention and treatment of acute complications during medical therapy. The long-term effects of chemotherapy are of less concern than those associated with high dose radiation therapy, because chemotherapy effects are reversible. In neutropenic patients, the risk of infection during medical therapy may require aggressive antimicrobial therapy and is potentially life threatening. Studies have shown that oral and periodontal assessment and management reduces the risk of infection and fever associated with oral conditions [24–28]. The clinical diagnosis of oral infection depends upon an accurate history of oral symptoms and a thorough examination. Signs and symptoms may be minimized in neutropenic patients, with reduced erythema, swelling, and pain in sites of infection. Careful appraisal of the cancer patient is needed, with understanding of pre-existing sites of periodontal involvement and careful evaluation including an assessment of tissue tenderness. While some have empirically raised concerns that periodontal probing, periodontal maintenance procedures and oral hygiene procedures may increase the risk of fever or bacteremia in leukemic patients, studies show that pre-treatment oral care and oral care during therapy results in reduced oral complications with no increase in risk of fever or bacteremia [24,25,27,29]. Therefore, comprehensive scaling and polishing of teeth, and professional supervision of oral hygiene and home-care are recommended.

The patient's underlying systemic disease and medical management are critical factors in determining the risk for infection. In patients with acute leukemia or chronic leukemia in blast phase, oral infection may be identified in approximately one-third of patients [30]. Ten per cent of patients receiving chemotherapy for solid tumors may develop oral infection [31,32]. The common complications in patients on intensive chemotherapy protocols for breast cancer (methotrexate, 5-fluorouracil, vincristine and prednisone) include: neurotoxicity (65%), mucositis (21%, often associated with neutropenia) and candidiasis [32]. In patients with blood dyscrasias, the frequency and severity of infection increases with the severity and duration of granulocytopenia [33–35]. Approximately one-half of adults with leukemia develop oral lesions during chemotherapy [34].

Bacteremia due to oral sources has been well documented in immunosuppressed patients [25,26,30,31, 34,36]. The bacteria implicated include periodontal flora, streptococci and staphylococci. More recently, an increase in *Streptococcal* bacteremia has been reported

in leukemic patients [34–41]. The shift in the organisms identified in bacteremia may be due to improved antibacterial coverage of gram negative organisms, which are routinely included as part of the chemotherapeutic protocols. Systemic antibiotic prophylaxis may have an impact on exacerbation of pre-existing periodontal disease. Gingivitis and periodontitis due to mixed bacterial infections are also common and have been reported in up to 25% of all infections in patients with acute non-lymphocytic leukemia [26]. Increased length of hospitalization and alpha-hemolytic streptococcal septicemia has been reported in patients with oral ulcerative mucositis consistent with an oral source of infection [36].

Patients with chronic periodontal disease receiving high dose chemotherapy may develop acute exacerbations from pre-existing sites of disease during periods of neutropenia [42–45]. Assessment of periodontal flora during chemotherapy showed a shift to increased gram-negative bacilli in less than 50% of patients [46,47]. Of these, *Pseudomonas* species predominated, although *Kiebsiella pneumoniae* was also present [48]. In another study, the periodontal flora was assessed in sites of symptomatic periodontal disease in leukemic patients [44]. Potential pathogens identified were *Staphylococcus epidermidis, C. albicans, S. aureus,* and *P. aeruginosa* in primary infection or mixed culture, that appear to represent exacerbation of chronic infection due to indigenous flora when compared with non-cancer patients. In these patients inflammatory signs were absent or minimal due to immunosuppression, making detection difficult [49,50]. Thus, pre-existing periodontal disease may serve as a source of infection in neutropenic patients [25,47,51]. An oral source of septicemia was suspected in 25% of acute leukemic patients who received dental care with scaling prior to chemotherapy compared to 77% among patients who did not receive dental care prior to chemotherapy [25]. The primary sources were pericoronitis or pre-existing periodontal infections. No difference in the incidence of fever or bacteremia were seen in a study of leukemic patients receiving or not provided with a probing assessment and scaling of the teeth [29]. Oral preventive care has been shown to not result in increased risk of bacteremia or in fever and is associated with less severe oral mucositis. Periodontal evaluation and treatment may reduce the severity of mucositis during treatment and reduce the potential for septicemia from periodontal sources [24], and should be a part of the management of patients at risk of neutropenia due to medical therapy.

Empiric antibiotic therapy for management of the febrile neutropenic patient is well established. The antibiotic must be broad spectrum, bacteriocidal, and given in appropriate dose and schedule. Metronidazole appears to be an important antimicrobial in management of oral infection associated with fever in neutropenic patients [52]. In leukemic patients, who remained febrile despite broad spectrum antibiotics, defervescence may occur when metronidazole is added to the antibiotic regimen [52]. The use of topical agents for prevention of colonization of the oropharynx and prevention of oromucosal infections has not yet been shown to be effective. Chlorhexidine has been shown to reduce plaque formation and disperse established plaque and may assist in managing gingivitis and periodontal involvement, reduce caries risk and may decrease oral colonization by Candida species [53,54].

Reactivation of latent Herpes Simplex Virus (HSV) occurs in the majority of carriers in the absence of viral prophylaxis in Ieukemia/HCT patients [55–60]. In the mouth the lesions most commonly affect the keratinized mucosa of the gingiva, palate and the tongue, frequently beginning on the attached gingiva as 1–2 mm rounded ulcerations that can extend to form large confluent lesions. Chemo-prophylaxis with acyclovir and acyclovir analogues has become standard for seropositive patients during hematopoietic cell transplant, since HSV infections in immunocompromised patients are severe [61–64]. Acyclovir-resistant HSV during prolonged acyclovir treatment has been reported, although when this occurs, increasing the dose of acyclovir or use of other antivirals such as foscarnet is available [55–69]. Varicellazoster infection is also common in immunocompromised patients with lesions initially confined to the dermatome distribution of involved nerve branches. Cytomegalovirus (CMV) causes up to 20% of post-transplant deaths, and reactivation occurs in up to 70% of seropositive patients [70]. CMV can present as persisting oral mucosal ulcers and has been reported to cause gingival enlargement [71–73]. Diagnosis requires suspicion of the potential causes of the lesion, and is based upon clinical findings, and positive virus identification in the involved tissue.

Elimination of pre-existing foci of infection prior to myelosuppressive chemotherapy is desired in patients who will become neutropenic. The oral cavity, dentition and periodontium must be examined thoroughly, including radiographic evaluation when indicated based upon the findings of the examination. If necessary, a delay in the myelosuppressive therapy should be considered in order to manage a symptomatic dental infection. If asymptomatic periapical pathosis is present, dental treatment may be completed after chemotherapy, and the patient should be covered with appropriate systemic antibiotics during myelosuppression [74–76]. Local irritants such as calculus and rough irregular dental surfaces should be managed to reduce local tissue irritation. Dentures should be cleaned regularly and removal of the appliance at night is recommended due to microbial colonization of the denture surface [77]. In cancer patients, pretreatment oral/dental management has been shown to decrease the length of stay, and to be

associated with reduced oral complications [77–80]. Good oral hygiene has been reported to reduce the risk of mucositis and to not increase the risk of fever or bacteremia [24].

In patients anticipated to become neutropenic, dental and periodontal treatment should be completed prior to chemotherapy (Table 1). It is desirable to have a 2-week healing period following dental surgery prior to the anticipated onset of neutropenia. In patients with solid tumors, chemotherapy may result in a short-term depression in white cell counts with recovery prior to the next course of chemotherapy. Dental and periodontal treatment should be provided when white counts are not suppressed, which is typically 2–3 weeks following a course of chemotherapy, prior to the next dose of chemotherapy. Antibiotic coverage may be considered when neutrophil counts are less than 500 cells/ml, if the treatment cannot be delayed until counts are higher than 1000 cells/ml.

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