

# Cancer therapeutics: an update on its effects on oral health

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With the increasing age of the American population, malignant diseases have also become more prevalent. While scientific advances have improved our understanding of the pathogenesis of these diseases, treatment and mortality have remained relatively unchanged. Various therapeutic methods for cancer have significant immediate and/or late effects on the oral cavity, and most of these effects require dental treatment modifications.

Under the large umbrella of malignancy, there are many different diseases with only two features in common: (i) a growth pattern outside normal cellular control mechanisms; and (ii) the ability to metastasize. Etiologies, treatments and prognoses for cancers are as varied as the diseases themselves. For example, whereas basal cell carcinomas of the skin are virtually 100% curable with simple local excision, acute leukemias require aggressive cytotoxic therapy, without which they are rapidly lethal in virtually 100% of the patients.

In this article we will restrict our focus to the more aggressive malignancies, which mandate toxic treatments that carry significant oral and systemic side effects. The afflicted patients are likely to require special oral care and significant dental treatment modifications. We will review the current evidence with special attention to issues relevant to the practicing periodontist, and will explore areas that remain controversial. Finally, we will make suggestions regarding the safe management of oral disease in this population.

## Epidemiology of cancer in the U.S.A.: demographic and etiologic factors

The annual incidence of cancer in the U.S.A. is estimated at 1.3 million (<http://www.cdc.gov/cancer/>

npcr/uscs/), and more than 11 million people worldwide suffer from malignant diseases. Various cancers have different age predilection and unfortunately children are not spared. However, the vast majority of malignancies are diagnosed in the seventh and eighth decades of life. Cancer is the number one cause of death in people over 85 years of age, but ranks a distant second behind cardiovascular disease in younger age groups. Thus, as life expectancy increases, the number of cancer cases also increases (31, 36).

In the U.S.A., approximately 500,000 people died of malignant diseases in 2004. At the top of the mortality list is lung cancer, which is closely followed by other solid tumors (breast cancer for women, colon and prostate cancer for men). African-Americans are disproportionately affected, for reasons that are still not completely understood. The age-adjusted death rate from malignant tumors at the start of the 21st century was almost the same as it was in the 1950s. However, the gender ratio has changed as a result of significant decreases in the incidence of cancer in men and steady increases in the number of women diagnosed with cancer (8, 31, 36). The reasons for this gender shift remain unclear (8, 31).

These epidemiologic data are not easily explained. Why, after five decades of scientific progress, are we still witnessing a death rate from cancer of about 200 per 100,000 people? Part of the reason may be the increased accuracy of diagnosis and maintaining better records. However, on a global assessment, treatments for malignant disease have not attained the level of scientific advance seen in the infectious and cardiovascular fields.

Many cancers have been associated with external factors, such as viruses, smoking, ionizing radiation, chemical toxins and ultraviolet light (28). A few others are associated with specific genetic mutations (35). Nevertheless, the vast majority of malignancies have remained classified as idiopathic. This fact

probably stems from the complexity and long duration of the malignant transformation process, which is not completely understood. Even the specific roles of the associated factors mentioned above have not been clarified (8), with most of the current information coming from epidemiologic studies that cannot establish specific mechanisms or cause–effect relationships (36). Recent advances in genetics and molecular biology hold the promise of unraveling this process, but only postulated theories are currently available regarding carcinogenesis.

## Cancer of the head and neck

A number of malignancies have been diagnosed in the tissues of the head and neck, from lymphoma to Kaposi's sarcoma, and from basal cell carcinoma to malignant melanoma. However, more than 90% of the cancers in this anatomical area are of squamous epithelial origin. Therefore, we will concentrate on this disease.

Squamous cell carcinoma of the head and neck is a malignancy that is strongly associated with tobacco smoking and consumption of alcoholic beverages (8, 28). The effects of smokeless tobacco are less clear and have been the subject of heated debate (48). Viruses, in particular those from the human papilloma virus family, may also play a significant role in the etiology of squamous cell carcinoma (28). Head and neck cancers represent *ca.* 3% of all malignant diseases in the U.S.A., with a relatively constant prevalence over the last few decades (36). More than 30,000 cases are reported each year in this country, of which *ca.* 70% are locally advanced at diagnosis. No major progress has been made regarding early detection or cure rates for squamous cell carcinoma. Advanced (Stage 3–4) disease has historically had a dismal prognosis. Survivors of squamous cell carcinoma typically have a poor quality of life as a result of surgical mutilation and/or other irreversible effects of therapy. Recurrences and second primary tumors are also common in the upper aerodigestive tract (15, 42).

## Cancer treatment today: therapeutic and palliative approaches

Standard therapeutic approaches to malignant diseases have remained relatively unchanged in the past half century. Other than surgical excision, which is

still the method of choice when the disease is localized, the strategy to combat cancer consists of targeting and destroying its rapidly dividing cells. Thus, high-grade disease will typically respond to therapy, while low-grade cancers are more indolent. Unfortunately, this strategy results in significant collateral damage, as normal cells that undergo mitosis are also killed.

The mainstay of cytotoxic treatment consists of ionizing radiation and chemotherapy. Both result in widespread cell death. Some of the important current advances in oncology have involved reducing selected detrimental effects of these cytotoxic therapies. The discovery of various cytokines has enabled reductions in therapy-induced bone marrow suppression, with its resulting immune dysfunction (7, 25). Colony-stimulating factors, such as granulocyte- and granulocyte–macrophage colony-stimulating factors, have significantly affected the severity and duration of granulocytopenia, whereas erythropoietin has resulted in increased numbers of red blood cells and decreased reliance on transfusions. Nevertheless, side effects caused by indiscriminate cell killing persist and continue to limit the dose of drug or radiation that a cancer patient can sustain (5, 13, 21, 46, 62).

A number of recent studies have described modest, but statistically significant, survival advantages when chemo- and radiotherapy are used concomitantly for various malignancies, including lung, breast, and head and neck cancers (1, 2, 15). Synergistic effects of these treatments are caused by the radio-sensitization of malignant cells by selected cancer drugs. However, this advantage comes at a cost, as combined therapy is also more toxic (62). For example, in the chemo-radiation of head and neck tumors, severe mucositis occurs in virtually every patient, leading to precarious nutrition and/or treatment interruptions. The patient's ability to maintain adequate oral care is also severely affected. These side effects contribute to the increased morbidity and cost associated with combined therapy (24, 62).

Other recent advances in cancer treatment include some new and more effective cytotoxic drugs, such as the taxanes (2), and progress in clinical applications of immune and molecular strategies (17, 54, 60). Research in this latter arena, known as the search for a 'magic bullet', or targeted therapy, aims at finding the still-elusive agent that will only eliminate the malignant cell and have zero or negligible effect on healthy tissues. The main candidates – selective immunity and biomolecular processes – have, to date, shown more promise in

the laboratory than at the clinical level. One notable exception is the introduction of Gleevec (imatinib mesylate) for treating chronic myeloid leukemia and possibly other malignancies (17). Gleevec contains a molecule that inhibits tyrosine kinase, which in turn prevents the formation of bcr-abl proteins necessary for leukemic cell reproduction. This drug can induce remission in *c.* 90% of chronic myeloid leukemia patients, with significantly fewer side effects than typical antineoplastic therapy. However, the side effects it does have can still prove intolerable to some patients. While significant, Gleevec is by no means a panacea. A number of tested cancers showed no response to the drug, and development of resistance to the drug in chronic myeloid leukemia patients has been reported (4, 17). Other targeted agents have also been approved for the market, but their efficacy has been modest and large clinical application will require further confirmation.

The main advance in radiation therapy for cancer consists of the development of computer technology that allows the multidimensional delivery of precise doses of radiation to the volume of the tumor. The computer controls the radiation beam and position, such that most of the energy is delivered to the cancer with minimal exposure to surrounding tissues. The combination of several intensity-modulated fields, coming from different directions, produces a custom-made radiation treatment to fit the specific anatomy of each tumor. This process is called Intensity-Modulated Radiation Therapy, and has allowed for substantial protection of radiosensitive normal tissues adjacent to malignant lesions. Thus, more effective radiation doses can be delivered with fewer side effects than conventional radiation techniques (37, 62).

## Oral effects of cancer treatment

### Chemotherapy

The mouth is highly susceptible to the toxic side effects of cancer chemotherapy. This is because of multiple factors, including a high turnover of oral mucosa cells, the presence of a diverse and complex microflora, and trauma to oral tissues during normal function (52, 53). The prevalence of chemotherapy-associated oral complications ranges from <10% in patients receiving adjuvant treatment, to 40% in those treated with primary curative chemotherapy, to over 80% in bone marrow

transplant patients receiving myeloablative regimens (25, 51, 53). The most common oral complications are mucositis, infection, pain, bleeding and taste disorders. Hyposalivation is also common in patients treated with chemotherapy (16), but the contribution of cytotoxic drugs to salivary dysfunction is, at present, unclear (14, 37, 46).

Virtually all these oral problems may lead to secondary events affecting the patient's overall health. For example, during immune suppression, the oral cavity can become a major source of systemic infection (9, 12, 23, 33, 44). Difficult and insufficient intake of food and fluids may result in dehydration and malnutrition (10, 11, 26, 40). Severe oral pain and dysfunction may have psychosocial consequences (21); patients may become depressive and isolated because of the inability to communicate and also because of the malodor which is often associated with oral dysfunction. Normal oral care is often restricted because of the associated pain and gingival bleeding (26).

Oral infection is a frequent complication of cancer therapy (6, 11, 25). There is considerable evidence that the oral microflora is a major source of systemic infection in immunosuppressed patients (11, 32, 44). Under normal circumstances, the mouth is home to more than 200 microbial species. As a result of treatment with antibiotics and chemotherapy, the host microflora equilibrium is altered. A shift towards higher numbers of pathogenic gram-negative bacteria is typically noted (6, 11). In the setting of mucositis, ulceration promotes colonization and overgrowth of indigenous, but also exogenous, hospital-acquired microbes. This scenario may lead to local and systemic infections at a time when the patient is most susceptible (32, 44). Hence, prophylactic oral care prior to, and during, cancer treatment is of utmost importance (22).

Once established, infection may, in turn, contribute to the increased severity and prolonged duration of oral mucositis (49). A damaged mucosal barrier may then act as a portal of entry for microorganisms to penetrate to the regional lymph nodes and/or into the bloodstream. The types of bacterial systemic infections that commonly affect neutropenic cancer patients have changed during the last two decades, with gram-negative rods gradually being replaced by gram-positive bacteria (70). Oral mucositis is the principal risk factor for bacteremia caused by viridans streptococci (23, 49). Although the majority of patients with this type of bacteremia have no manifestation of infection other than fever, some may develop an acute respiratory distress syndrome and

septic shock, especially following bacteremia with *Streptococcus mitis* (23).

Infections of oral origin are also associated with a wide variety of other microorganisms, including anaerobic bacteria (6), fungi and viruses (47). Virtually all of these may give rise to systemic infectious complications. In a number of cases, the appearance of the lesions, including size and color, may contribute to the differential diagnosis (25).

Chronic infections associated with the oral cavity may also give rise to complications during immune suppression. These infections typically involve the dental pulp/peri-apical area, impacted teeth, and the periodontium (11). Periodontal infections, in particular, may represent a source of systemic infection in neutropenic cancer patients (3, 45). The contribution of chronic periodontitis to systemic infections is probably underestimated (29). This disease where the microorganisms are located deep in the periodontal tissues is seldom painful and cannot be diagnosed by visual inspection alone (45). Additionally, in neutropenic patients, inflammation is typically minimal and thus the disease can be easily overlooked. Nevertheless, chronic periodontitis is characterized by loss of the tooth-supporting tissues, and deep pockets may be formed in the affected area (65).

Diseased periodontal tissues harbor a biofilm containing a variety of microorganisms, including gram-negative strict or facultative anaerobes, streptococci, coagulase-negative staphylococci, enteric rods, *Pseudomonas* spp., *Candida albicans* and herpesviruses (3, 6, 27, 29). Proportional increases of subgingival microorganisms can occur during intensive chemotherapy (45). These microorganisms, cell wall substances and host inflammatory products (e.g. pro-inflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor- $\alpha$ ) continuously enter the bloodstream and the lymphatic circulation via disrupted pocket epithelium and elicit a systemic immunologic and inflammatory response (18, 27, 34, 45). Animal studies of experimentally induced periodontal infections suggest that cytotoxic agents contribute to the loss of subgingival epithelial integrity and induce a decrease of neutrophils in the periodontal tissues (65). More bacteria invade the periodontal tissues in animals receiving myelosuppressive agents compared with animals receiving placebo. Similarly, patients who were treated with intensive chemotherapy and also had severe chronic periodontitis experienced more febrile episodes than those with a healthy periodontium (45, 46). In addition to systemic spread via the vasculature, noxious substances from periodontal pockets can flow freely into the oral cavity

and may contribute to oral mucosal, respiratory and gastro-intestinal inflammation and infection.

## Long-term complications

Most chemotherapy-induced oral complications are acute and resolve spontaneously after the cessation of cytotoxic treatment. Only a few studies have reported late oral sequelae of chemotherapy in adult cancer patients (38). In allogeneic bone marrow transplant patients, chronic oral graft-vs.-host disease may develop. The lesions often have a lichenoid clinical appearance (hyperkeratotic striae, papules and plaques), and may be associated with erythema and ulcerations. Additionally, there may be a Sjögren-like oral-ocular sicca syndrome characterized by progressive salivary gland atrophy and hyposalivation (67). Although one would expect that these patients may be at increased risk for dental caries and periodontal disease, there are presently no data to support that notion. Conversely, periodontal infections may result in a flare of oral graft-vs.-host disease, or complicate its management. There is also evidence indicating that osteoporosis, which is a common complication in cancer patients (38), is an additional risk factor for bone loss in periodontitis patients.

More extensive data are available on late oral sequelae of cytotoxic treatment for childhood cancers. Increased dental caries activity following cytotoxic therapy has been reported in children with active caries at the time of cancer diagnosis (43). Intensive chemotherapy for childhood cancer may also induce developmental disorders of the dentition, such as missing or small teeth, shortened roots and enamel defects. In addition, growth and developmental abnormalities of the jaws and other craniofacial structures are common in these patients, particularly for those treated at a very young age (20). Chemotherapy is also associated with an increased risk of second malignancy, including oral squamous cell carcinoma (19, 30). It is therefore important that dental professionals become aware of this risk and closely follow the patient's status after chemotherapy.

## Radiation therapy

Despite the advent of Intensity-Modulated Radiation Therapy, the side effects of ionizing radiation remain severe, often necessitating treatment interruptions (57). Typical tumoricidal doses range from 30 to 80 Gy delivered to the tumor volume, and 20–50 Gy given to the adjacent tissues. Most radiation treatments are delivered through linear accelerators in

200 cGy daily portions for 5 days per week. Hyperfractionated regimens consist of two daily doses of 180 cGy, require less time to complete, but are generally marred by worse mucosal side effects.

The mouth is affected by ionizing radiation only when it is in the field or the vicinity of areas where radiation is aimed. The principal oral complications consist of damage to the mucosa, salivary glands and feeding vessels. Vascular damage occurs at cumulative doses of 20–30 Gy, whereas clinical mucositis starts at *ca.* 40 Gy and worsens throughout the duration of therapy. Salivary gland function is impaired from the beginning of the treatment; this impairment becomes permanent in most patients treated with > 50 Gy. Patients whose salivary glands have been irradiated with ≥60 Gy are virtually devoid of any function (37, 56).

Endothelial cells are susceptible to the effects of radiation and respond almost immediately with cytokine production and altered morphology (48). Vascular leakage is one of the first phenomena to occur in response to ionizing radiation and, in turn, results in the accumulation of inflammatory substances and tissue edema. After extended exposure, affected vessels, particularly larger ones, undergo a process of fibrosis and gradual narrowing that may lead to outright obliteration. This process is neither preventable nor curable and often results in ischemia or infarction and tissue necrosis. Osteoradionecrosis has been reported to occur in 2–11% of head and neck cancer patients treated with ionizing radiation (56). This pathologic development may be important for the dentist, particularly when the mandible is in the field of radiation, as it has denser bone and little collateral circulation. Tooth extraction or other invasive procedures may expose the dead bone to the oral environment, leading to infectious processes that are difficult to treat and may be subject to rapid progression (65).

Radiation-induced oral mucositis is another dose-dependent phenomenon, but this side effect dissipates with cessation of the insult. Unlike its chemotherapy-induced counterpart, the patient here is seldom immunosuppressed, so the risk and consequences of infection are less significant. Nevertheless, mucositis can be the dose-limiting step in head and neck radiation therapy because of the severe pain associated with it. Nutrition and speech may become impossible and the patient may require hospitalization for parenteral nutrition (25, 26).

The effect of ionizing radiation on salivary glands is not well understood. Secretory cells of the acini do not replicate and thus should be relatively radio-resistant. Nevertheless, secretion begins to diminish soon after the inception of therapy, and the

deficiency becomes permanent after *ca.* 40 Gy (37). Hyposalivation leads to further difficulty in speech and nutrition and in the long-term it allows unchecked growth of opportunistic pathogens. Oral candidiasis and rampant caries are common repercussions of salivary hypofunction (37).

Other late oral effects of ionizing radiation include taste loss, tissue fibrosis and limitation of jaw mobility (62, 64). Radiation-induced genetic mutations that do not lead to cell death may predispose the patient to additional malignant transformation. Nevertheless, in many cases, radiation therapy may be less morbid than surgery by preserving tissues with essential function (organ preservation).

Another mode of radiation delivery is through implantation of radioactive elements in the tumor bed, which typically results in fast, extensive necrosis of all tissues within the vicinity of the implant. A variant of the implantation method is known as brachithery and is accomplished through the surgical positioning of a hollow tube in the tumor mass. Radioactive elements (typically Iodine<sup>125</sup>) are passed through the tube daily and deliver 180–300 cGy doses. The advantages of implantation are that the volume of normal tissue affected is generally smaller and that larger doses of radiation can be delivered to the malignancy. The main disadvantage of the procedure is that all tissues within the affected volume undergo rapid necrosis. Thus, tumors adjacent to bone, major vessels or other vital structures are not good candidates for this type of therapy.

## Oral management considerations

### Pretreatment phase

Oral complications in cancer patients can be reduced when pre-existent oral infection and the oral bacterial load are reduced prior to cancer treatment (22, 32). Evaluation and management of patients scheduled to undergo intensive therapy should occur as early as possible. The overall goal is to eliminate or stabilize oral diseases, or other conditions that could produce complications during or following cancer therapy, expeditiously. It is evident that this requires adequate communication with the medical team, in particular when patients have poor oral health and/or are frail because of their medical condition.

The medical team should clearly advise the dentist about the oncology treatment plan, risk for cancer-therapy related complications, and available time to the onset of neutropenia, current medications and the

patient's medical status. In turn, the dental team should develop a plan for oral disease management before, during and after cancer therapy, and communicate this to the medical team. In patients with poor oral health who require immediate initiation of cancer therapy, the benefit of performing dental interventions should be weighed against potential disadvantages, such as the risk for incomplete healing (55). However, in selected cases where oral disease poses an imminent danger, postponing the cytotoxic treatment may be a reasonable consideration. Regardless, the medical team should be informed about possible oral sources for infectious complications during therapy. Intervals between chemotherapy cycles provide an opportunity to complete medically necessary oral and dental care. For radiation patients, the first 3–6 months after therapy cessation represent a last window of opportunity for lower osteoradionecrosis risk after invasive dental treatments (68).

Currently there are no widely accepted guidelines, with respect to prophylactic antibiotic coverage, prior to invasive dental procedures in immune-deficient cancer patients. In patients with a neutrophil count of  $<1000/\text{mm}^3$ , or in patients with chronic indwelling venous access lines, the protocol of the American Heart Association for infective endocarditis is empirically recommended. When an invasive procedure is unavoidable during profound neutropenia (neutrophil count  $< 500/\text{mm}^3$ ), a more aggressive antibiotic approach (broader spectrum parenteral agents) may be indicated. In thrombocytopenic patients, platelet infusions, before and during healing from invasive procedures, may be necessary. Extractions should be carried out as atraumatically as possible and with primary socket closure (57, 66).

The patient and their carers should be informed about the oral complications that may develop during cancer therapy and the rationale for maintaining optimal oral hygiene and avoiding oral trauma. Oral hygiene instruction should be geared specifically to the individual situation and needs of the patient. Tooth brushing can be safely performed with a soft brush. To avoid bacterial overgrowth, the toothbrush should be rinsed well and be air-dried between uses. Patients who have used dental floss or other interdental cleansing devices prior to therapy should continue to do so, but should be instructed how to perform the intervention correctly in order to avoid mechanical injury.

For detailed oral management protocols for cancer patients we refer the reader to: <http://www.nci.nih.gov/cancerinfo/pdq/supportivecare/oralcomplications/healthprofessional>.

## During therapy

During cancer therapy, keeping the oral tissues moist with bland rinses, reinforcing oral hygiene and avoiding trauma, are important considerations. In most cancer centers, the oncology nursing team plays a key role in providing and supervising oral care during hospitalization (46). The mouth should be inspected daily, preferably with a halogen light source, to detect oral complications at an early stage. Myelosuppression *per se* is no contraindication for oral hygiene measures, but if the patient's condition does not allow manipulation in the oral cavity, antimicrobial rinses containing chlorhexidine or povidone iodine should be prescribed. The use of chlorhexidine to prevent or treat oral mucositis is not supported by the literature, but there is convincing evidence for the effectiveness of this broad-spectrum antiseptic in inhibiting the accumulation of dental plaque (51). In addition, chlorhexidine rinses have antifungal properties (46). Prophylactic antiherpetic regimens may be beneficial to herpes simplex virus-seropositive patients receiving intensive chemotherapy. Bergmann (11) found that oral administration of acyclovir reduced the incidence of clinical oral herpes simplex virus lesions as well as the isolation of herpes simplex virus type 1 from saliva. Similar results have been reported in hematopoietic stem cell transplant patients (25).

Recent studies have provided new hope for the prevention and treatment of chemotherapy-induced mucositis. Animal research and one clinical trial have demonstrated that keratinocyte growth factor-I can reduce the incidence and severity of mucositis in patients treated with intensive chemotherapy, without affecting the outcome of cancer (54). Similar studies are in phase III of development with other groups of patients, including head and neck cancer. If validated, keratinocyte growth factor-I will become the first effective prophylactic/therapeutic agent for the condition.

Adequate pain management is imperative and in patients with severe mucositis, opioids are the agents of choice. The overall efficacy of topical anesthetics (such as viscous lidocaine or benzocaine) to manage mucositis has not been systematically studied. Their usefulness is probably limited to only mild-to-moderate mucositis pain (26). Prophylactic oral cryotherapy is recommended in patients specifically receiving bolus 5-fluorouracil chemotherapy to prevent mucositis. In addition, low-level laser therapy may be effective in preventing and ameliorating mucositis in patients receiving high-dose chemotherapy, but requires expensive equipment (46, 54).

If a neutropenic patient becomes febrile, it should be realized that besides mucositis, infections related to the dentition may also be the cause. Partially erupted teeth may be a nidus for infection (pericoronitis) (57), and peri-apical and periodontal infections may flare up (3, 45). These infections are typically painful and accompanied by tenderness of the affected area. Pre-existent oral infections, particularly periodontitis, are also capable of inducing fever and systemic infections, but without clear signs and symptoms of inflammation. It is thus imperative that the oral condition be assessed prior to initiation of cytotoxic treatment and that the oncology team is cognizant of (residual) periodontal infection. Antimicrobial agents directed to periodontopathic anaerobes should be included in the empiric antibiotic regimen in such patients (45).

Spontaneous oral bleeding, associated with thrombocytopenia, is usually managed with platelet transfusions; topical application of agents is also helpful and can include vasoconstrictors, clot-organizing materials (tranexamic acid, thrombin, collagen products), fibrin glue, tissue protectants (e.g. cyanoacrylate products) and agents to counteract clot breakdown (e.g. aminocaproic acid).

In addition to the management of mucositis and nutrition difficulties, the radiation patient may benefit from sparing of healthy oral and para-oral tissues. Limitation of radiation effects to the parotid glands may provide the possibility of maintenance of adequate salivary secretion. Protecting the submandibular glands can also alleviate post-treatment hyposalivation, albeit to a lesser extent. Leaded blocks can accomplish this purpose when feasible. The use of sialogogues, such as pilocarpine, during radiation has also been proposed (69), but confirmatory studies are needed. Recently, the American Food and Drug Administration approved amifostine for use with ionizing radiation for maintaining salivation. Amifostine has some significant side effects (including severe nausea and hypotension) and its effects on salivation are moderate at best (65). Subcutaneous use appears to reduce some of the side effects, but its efficacy requires confirmation.

### **Post-treatment phase and long term follow-up**

In the chemotherapy patient, the frequency and severity of acute oral complications typically decreases concomitantly with hematopoietic recovery. Nevertheless, it may take considerable time for the mucosal immune defense mechanisms to recover

fully and many patients continue to be at risk for infection, particularly from opportunistic pathogens (25, 46). In hematopoietic stem cell transplant patients, particularly those treated with allogeneic transplants, immune reconstitution may take longer than a year and antiviral prophylaxis is extended until full immune recovery (40, 46).

The frequency of dental check-ups and preventative measures (e.g. professional cleaning and fluoride regimens) should be geared to the needs of the individual patient in relation to the immune status. In patients with chronic oral graft-vs.-host disease, invasive oral procedures should be avoided until the patient is stable (69).

As discussed above, long-term survivors of high-dose chemotherapy, including autologous hematopoietic stem cell transplantation, will generally have few significant chronic oral complications. Salivary problems in these patients are seldom permanent. However, the oral health implications of developmental and growth disorders in survivors of pediatric malignancies, as a result of cancer treatment during early childhood, can be significant (19, 20, 30). Growth hormone therapy may have a beneficial effect on the development and function of the craniomandibular complex (20).

Radiation therapy to the head and neck typically has lifelong consequences. Patients treated with ionizing radiation doses of  $> 40$  Gy will suffer from chronic hyposalivation and its resultant effects on dentition and soft tissues. If residual salivary secretion exists, it can be maximized by the use of sialogogues, such as pilocarpine (Salagen) or civemiline (Evovac) (37). Patients with no gland function remaining can benefit from artificial saliva or other liquids that maintain oral moisture and help with debris clearance. Lemon-tasting candy, even when sugarless, is acidic and is contraindicated in dentate patients. Additionally, these patients should be provided with high-level fluoride dentifrices or other topical fluoride gels to protect from carious activity.

Frequent recalls for prophylaxis and close follow-up is important in order to maintain dental integrity and avoid further complications. Invasive procedures in radiation patients will always create the possibility of infection of necrotic bone, particularly the mandible. The risk of osteoradionecrosis does not diminish with time, and all dental extractions performed longer than 6 months after radiation therapy should be considered high risk. Prophylactic antibiotic use in these cases is controversial because penetration of necrotic bone is unlikely. Careful surgical technique followed by primary closing, with copious antimicrobial rinsing

during the procedure, are imperative (68). If infection of bone does develop, conservative treatment with topical antimicrobials and removal of sequestered fragments is recommended (68).

## Dental implants in cancer patients

The main questions regarding dental implants in cancer patients refer to the effect of cancer therapy on established implants and implant placement in the cancer-treated patient. There are significant differences in the answer to these questions based on the type of cancer therapy (radiation vs. chemotherapy).

### Chemotherapy

As may be expected, the interference between chemotherapy and dental implants has not been extensively studied and appears to be minimal. There are no reports on pre-existing implant failure as a result of subsequent chemotherapy. One case report (41) and one retrospective study (39) described uneventful osseointegration of implants placed at the time of cancer surgery, which was followed by adjuvant chemotherapy. Thus, it appears that osseointegration can occur despite cytotoxic treatment in the post-operative period. Although there is no scientific validation, there is little reason to expect that implants placed in chemotherapy-treated cancer patients in complete remission would have worse outcomes. As always, surgical precautions must apply, and the surgeon must verify that the patient's immune parameters are adequate in order to avoid peri-operative infection and to ensure uneventful healing. If the number of neutrophils is close to normal, we see no reason for the need of antibiotic (pre)medication or other extraordinary measures.

### Ionizing radiation

As ionizing radiation can induce ischemia in osseous tissues, the issue of dental implants in irradiated patients is significantly more complex. It is well known that even without surgical procedures, irradiated bone is prone to necrosis, particularly in the denser and less vascularized mandible. Thus, it would seem logical that placement of implants in such jaws is not advisable. Nevertheless, current literature reflects a different picture, albeit weak and controversial.

The irradiated patient presents a multitude of confounding variables: (i) the radiation dose is not

evenly distributed over the jaw bones, and therefore while some areas may receive as much as 70 Gy, other areas may receive no radiation; (ii) a significant number of cancer patients have parts of their jaw surgically removed, which may further impair circulation to the remaining segment; (iii) some patients may be reconstructed with autologous grafts, with or without vascularization; and (iv) vascular obliteration continues in irradiated bone long after the cessation of therapy. Therefore, the site of the implant and timing of placement are extremely important and the outcomes of some implants may not be generalized or extrapolated to others. Unfortunately, we could not find any prospective, randomized clinical trial on the subject. With this preamble, we present data from some retrospective studies.

Werkmeister et al. (63) analyzed implant survival in 29 irradiated squamous cell carcinoma patients and reported 31.2%, 26.7% and 14.7% implant loss in grafted, irradiated and nonirradiated bone, respectively. These implants were placed *ca.* 18 months after therapy, at a time when the vasculature would show the greatest amount of damage. These findings were echoed in another study (66), where the implant survival percentages were 54%, 72% and 95% in grafted, irradiated and nonirradiated bone, respectively. Analyzing similar variables, Visch et al. (58) also concluded that implant survival was influenced by location, bone resection and irradiation dose. Overall implant survival was 78% in this study, but as low as 59% in the irradiated mandible.

In a similar study, Weischer and Mohr (61) added yet another variable: the type of prosthesis. Although these authors also reported a poorer survival of implants in irradiated than in nonirradiated patients, they were able to raise the success rate in the former group from 75% to 86% by avoiding implant-tissue supported prostheses. The higher percentage was obtained when irradiated patients were restored with prosthetic devices supported solely by implants. The authors attribute the better outcome to the avoidance of soft tissue trauma from prosthetic devices.

Thus, it appears that implantation of grafted bone has the poorest outcomes, and the success of implant placement in irradiated bone is dependent on the amount of radiation. Soft tissue trauma produced by prostheses can also negatively influence the longevity of implants.

By contrast with the above studies, one group of researchers (59) described a 97.9% success rate at 5 years for implants inserted in mandibles pre-irradiated with 60 Gy. Neither the site of implantation, nor



the time of surgery, had any effect on osseointegration. This was a relatively small retrospective study and its discrepant results must be interpreted with caution.

Finally, the effect of radiation on pre-existing implants was described in an article by Schepers et al. (50). The rate of osseointegration was virtually the same for irradiated vs. nonirradiated patients (97% and 100%, respectively), and the authors concluded that postoperative radiotherapy does not affect the success of dental implants. These results must also be interpreted with caution, as all implants were placed in the mandibular symphysis, the follow-up was relatively short and successful osseointegration was not defined. Larger, preferably prospective, trials are necessary to confirm these findings.

## Conclusion

Oral consequences of cancer therapies are varied and their morbidity can be high. The mouth can be a source of life-threatening infection and oral pain can lead to malnutrition and treatment interruptions during cancer therapy. The dental team can have a salutary role and must work closely with the oncologists to prevent, treat and follow up oral disease in these unfortunate patients.

Diagnosis and treatment for oral disease should ideally be accomplished prior to initiation of cytotoxic therapy, and the dental team should follow the patient during treatment and advise the medical team if oral conditions develop. In general, it appears that dental and periodontal therapy can be undertaken safely for survivors of cancer. Placement of implants is also safe in chemotherapy-treated individuals. However, more study is necessary to determine benefits and risks, as well as the ideal parameters for implantation of irradiated jaws.

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