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The acute effects of chemotherapy upon the oral cavity: Prevention and management

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The oral and dental complications arising in cancer patients can be attributable to the malignant disease itself and to the various modalities of cancer therapy. Up to 40% of all patients receiving cancer chemotherapy develop acute oral complications. Oral complications may result in significant morbidity, impaired nutrition, treatment delays, and dose reductions which are affecting the prognosis of the primary disease. Many investigators have developed a series of clinical trials designed to study treatment modalities for these pathologic processes. These trials have demonstrated clinically helpful therapies and also have demonstrated lack of benefit for other proposed treatments. In this article we aimed to assess acute oral complications in cancer patients due to chemotherapy and review the recent treatment modalities for prevention and management of those complications since these changes in physiologic process are still problems that need further investigation. [Turk J Cancer 2001;31(3):93-105]

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Oral complications are frequently encountered in patients receiving anticancer therapy and these complications may result in significant morbidity, treatment delays, dose reductions, and nutritional deficiencies (1-3). Intensive combination chemotherapy protocols, high dose chemotherapy regimens and allogeneic bone marrow transplantation are being increasingly used in the treatment of both lymphoproliferative malignancies and solid tumors (4). Ideally, a chemotherapeutic agent should only destroy malignant cells. Unfortunately, anticancer drugs with such a sparing effect on normal tissues are not yet available and therefore, some damage to normal tissues is inevitable, particularly those in which rapid cell division normally occurs (i.e., hair, skin, mucous membranes and the hematopoietic system).

The type of chemotherapeutic agent(s), the dosage, and the frequency of drug administration are important therapy related factors which affect the development of stomatotoxicity (5,6). Chemotherapeutic agents that have a high potential for precipitating oral mucosal damage are alkylating agents such as busulfan, cyclophosphamide, procarbazine, and thiotepa; anthracyclines such as daunorubicin, doxorubicin, and epirubicin; antimetabolites such as cytosine arabinoside, hydroxyurea, 5-fluorouracil, methotrexate, 6-mercaptopurine, and 6-thioguanine; antibiotics such as actinomycin D, amsacrine, bleomycin, and mitomycin; vinca alkaloids such as vinblastine and vincristine; and taxanes (7,8). The direct inhibitory effects of chemotherapy on DNA replication and mucosal cellular proliferation result in a reduction in the renewal capacity of the basal epithelium and therefore, the direct stomatotoxicity of the chemotherapy occurs. These events are believed to result in mucosal atrophy, collagen breakdown, and eventual ulceration (9-11). Chemotherapeutic agents also cause thrombocytopenia and leukopenia disturbing the hemostatic and immune-mechanisms of the patient (12). Thus, chronic dental pathologic conditions such as periodontal disease and dental pulp involvement may lead to some important acute problems during chemotherapy. Thrombocytopenia may precipitate spontaneous profuse bleeding from the periodontium, especially in patients with existing periodontal disease (6,13).

On the other hand, a variety of patient-related factors also appear to increase the potential for developing oral complications, including the age of the patient, nutritional status, type of malignancy, pretreatment oral condition, oral care during treatment, and pretreatment neutrophil counts (14-16). Younger patients appear to have a greater risk of chemotherapy-induced stomatitis, probably due to a more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors (16,17). Patients who have hematologic malignancies, preexisting poor oral hygiene and periodontal disease, poor nutritional status, and low neutrophil counts show an increased incidence of oral complications following chemotherapy (16,18,19). A recent study showed that the overall incidence of oral complications in children receiving high dose chemotherapy was 42% with the highest incidence in children with acute leukemias and non-Hodgkin's lymphomas (20).

The acute effects of anticancer chemotherapy upon the oral cavity include mucositis, infection, hemorrhage, xerostomia, neurological disorders, and nutritional deficiencies (18,21-23).

Mucositis

Mucositis is a common dose-limiting complication in patients receiving systemic anticancer chemotherapy, bone marrow transplantation, and local irradiation for tumors in the head and neck area. It appears clinically as erythematous or diffuse ulcerative lesions (15,16,24). Chemotherapy-induced oral mucositis may cause considerable patient morbidity and its prevalence has been reported as ranging from 30% to 39%, although a prevalence as high as 75% has been reported with 5-fluorouracil (25). Patients receiving curative head&neck irradiation are the most susceptible ones and children undergoing chemotherapy are three times more likely to be affected (26-28). Oral mucosa is

comprised of membranes of a high mitotic index with rapid epithelial turnover and maturation rates. This causes the mucosa to be vulnerable to the adverse effects of chemotherapy (15,25,29).

Even though there are variable grading systems of mucositis, the guidelines recommended by World Health Organisation have been used most frequently (Table 1) (16). Mucositis develops in four phases; an initial inflammatory/vascular phase; an epithelial phase; an ulcerative/bacteriological phase and a healing phase (15). Depending on the chemotherapeutic regimen used, erythematous mucositis develops in 3 to 5 days after the initiation of therapy and ulcerative mucositis in approximately 7 days (21,30-32). Mucositis initially precipitated by chemotherapy may become aggravated by local irritants such as jagged teeth, accumulation of calculus and plaque, defective dental restorations, and dental prostheses (18,23,33). These painful ulcerative lesions are noted primarily on nonkeratinized tissues, such as the buccal and labial mucosa. The ventrolateral surface of the tongue is rarely subject to mucositis but may become painful (30,31). The chemotherapy alters the integrity of mucosa, the microbial flora which normally inhabit the oral cavity, salivary quantity and composition, as well as the epithelial maturation (17,29). Since intensive chemotherapy reduces the granulocyte counts to very low levels, mucositis may persist for weeks, and it may cause additional problems in the follow-up of the patient, such as significant pain, dysphagia, alteration in nutritional status, and risk of infection (16-18,23). Among those problems, the most important one is the risk of infection; mucosal ulceration may become a portal entry for the invasion of pathogens that in turn may be life threatening (21,23,34). Preventive measures and treatment of established oral mucositis will be discussed later.

Table 1
World Health Organization Grading of Mucositis/Stomatitis

Grade	Symptoms
0	None
I	Painless ulcers, erythema, or mild soreness
II	Painful erythema, edema, or ulcers, but can eat
III	Painful erythema, edema, or ulcers, but cannot eat
IV	Requires parental or enteral support

Bacterial Infections

Bacterial infections often contribute to morbidity and mortality in immunocompromised patients (35,36). A wide range of bacteria, including odontopathic, periodontopathic, and transient pathogens of the oral flora may manifest as ulcerative lesions (37-39). Coagulase-negative staphylococci and streptococci originating in the mouth are increasingly recognized in immunocompromised patients as a source of bacteremia and septicemia (40-44). As a result of immunosuppression, the mouth may also be inoculated by Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Salmonella enteridis, anaerobes, and other opportunistic

organisms (30,42,45). In those patients, frequent rinses with saline or bicarbonate solutions, gentle debridement, and systemic beta-lactam antibiotics may be of benefit. If mucositis is severe and the patient is neutropenic, additionally, oral antiseptic solutions and systemic anaerobic therapy is recommended (16,23).

Fungal Infections

The incidence of fungal infections has been reported as being as high as %40 in patients with hematologic malignancies (43). Fungal infections in immunocompromised patients most commonly involve Candida albicans (46,47), but Candida krusei has also been implicated (48). Superficial white plaques on the oral mucosa should remind oral candida infection. In neutropenic patients, oral Candida infections may cause systemic infections, with high mortality (47). Intraoral and esophageal candidiasis may be treated effectively with nystatin or clotrimazole troches (49). Recurrent infections, however, are common during treatment (50). Per oral fluconazole or amphotericin B, administered prophylactically, have also been reported to reduce the incidence of superficial infections (23,51). Intravenous amphotericin B, however, is the preferred drug for treating serious systemic fungal infections (52).

Viral Infections

In patients receiving anticancer chemotherapy, secondary infection of the oral mucosa with a number of viruses, including Herpes simplex virus (HSV), Cytomegalovirus, Varicella zoster and Ebstein Barr virus may develop (16,23). Since the early 1980s, the medical and dental literature has documented variably the incidence of mucocutaneous HSV infection in immunocompromised patients; in patients who developed mucositis after chemotherapy, 37% to 68% of cultures from oral lesions demonstrated HSV (53-56). HSV produces large, painful ulcerations which tend to heal slowly. The presence of lesions on the lips or a yellowish membrane covering extremely tender ulcerations may help distinguish oral HSV infection from uncomplicated mucositis, but laboratory testing is often required (57). High dose intravenous or oral acyclovir is effective for the treatment of systemic HSV infections, with foscarnet as an alternative (56,58-60). For localized mucocutaneous HSV infection, intravenous acyclovir 5mg/kg every 8 hours for 7 days is sufficient (16). Acyclovir solutions used in combination with chemotherapy is gaining acceptance as a prophylactic measure in susceptible patients (59,60).

Hemorrhage

Chemotherapeutic agents may secondarily induce thrombocytopenia, which is the usual cause of intraoral hemorrhage (36,61-63). Hemorrhages may present clinically as gingival bleeding or submucosal bleeding with hematoma formation. Profound thrombocytopenia ($<20X10^9/L$) causes most of these changes (30,31,36). Petechial hemorrhages are often seen in the gingiva, buccal mucosa, tongue, floor of the mouth, and hard and soft palate. Ecchymosis is more likely to be found in the tongue and floor of the mouth (23). Prevention is the most effective technique used to avoid hemorrhage.

Eliminating potential areas of trauma (sharp restorations, fractured teeth) and preexisting intraoral disease before chemotherapy minimizes hemorrhage. When severe thrombocytopenia is present, the patients should use soft brush and eat pureed or liquid food. Minor oral bleeding can usually controlled by pressure, but major oral bleeding may need platelet transfusions. Procedures such as the extraction of the teeth or periodontal surgery should not be done when platelet counts are below $<40X10^9$/L (23).

Xerostomia

Pretreatment xerostomia may lead to a decrease in oral pH, and with the lowering of pH, the normal buffering mechanism for lactic acid is lost, dental enamel may decay, and gingivitis may result (64). Head and neck radiotherapy is a frequent cause for xerostomia in cancer patients; on the other hand, a variety of drugs other than chemotherapeutics are prescribed for cancer patients like sedatives, opiates, antidepressants, antihistamines, diuretics which may also cause xerostomia (65). Altered salivary flow and salivary histatin levels may be important predisposing factors to oral candidiasis (66) and reduced salivary amylase and IgA levels may be associated with an increased incidence of oral infections with opportunistic bacterial pathogens (67). Patients with xerostomia, whose salivary glands can respond to stimulation may benefit from using simple dietary measures such as eating carrots or celery or by chewing sugarless or xylitol-containing gums (16,23,65).

Neurologic Complications

After administration of vinca alkaloids (vinblastine and vincristine), chemotherapy-induced neuropathy may occur and this may affect the oral cavity with pain or paresthesia symptoms (30,31,61). Often the clinical and radiographic examinations in these cases are unremarkable, and the symptoms of neurologic complications may disappear after the chemotherapeutic agent is discontinued (30,61).

Inadequate Nutrition

Chemotherapy also causes nutritional problems (68,69). The cytotoxic effects of chemotherapeutic agents on the oral mucosa predispose the patient to pain, difficulty in mastication, and dysphagia caused by atrophy of the mucosa, which leads to mucositis and ulceration. Altered or reduced taste sensation is also common, and the use of topical oral medications may be unpleasant to the patient (68). Nutritional support is important to avoid nutritional deficiencies and overt malnutrition. Well-cooked and small pieces of food in liquids, cooked cereals, pureed meats and vegetables, scrambled eggs, puddings, large amount of liquids, and low acid fruits are recommended, but foods which are dry, spicy, salty, hot, or citrus are not recommended (16,69,70). Smoking and alcohol use should be avoided. In a patient with severe oral complications, nutritional supplements with high calories or parenteral feeding can be given (71).

Recommendations for prevention and management of oral complications

According to the National Institutes of Health consensus conference statement (19), all cancer patients should have an oral examination before initiation of cancer therapy and treatment of pre-existing or concomitant oral disease is essential in minimizing oral complications. The potential oral sequela associated with chemotherapy can be prevented, reduced, or alleviated with careful and continuos dental care (72). Tooth brushing with a soft brush should be continued where possible throughout the therapy (72). However, optimal plaque control is difficult to achieve, especially given the physical and emotional demands on cancer patients. Prevention and management of oral complications in cancer patients should employ a team work, including clinicians, dentists, oncology nurses, and nutrition specialists. Direct family involvement in patient care is encouraged for maximum treatment compliance (16).

Some preventive measures have been tested in an attempt to reduce chemotherapy-induced oral mucositis: 1. Alteration of the mucosal delivery and excretion of individual chemotherapeutic agents; 2. Modification of the epithelial proliferation capacity; and 3. Reducing the potential for infectious or inflammatory complications (16).

To alter the mucosal delivery and excretion of individual chemotherapeutic agents, some agents and local preventive measure had been used in clinical trials with conflicting results. Cooling of the oral mucosa with ice (cryotherapy) for 30 minutes during chemotherapy produces temporary vasoconstriction, thus reducing the delivery of drug to the oral mucosa. A 50% reduction in oral mucositis was obtained in patients who received 5-fluorouracil with oral cryotherapy (73,74). Allopurinol inhibits the activation of 5-fluorouracil to fluorouracil monophosphate, thus diminishing the stomatotoxicity, but the effect of Allopurinol mouthwashes is still controversial, since contrary results have been reported in literature (75,76). There was a reduction in the incidence and severity of mucositis in the patients who received an anticholinergic agent, propantheline, to reduce the high dose etoposide related mucositis by decreasing the salivation and xerostomia, and thus blocking the excretion of etoposide in saliva (77). Leucovorin rescue after high dose methotrexate infusion prevents patients from severe stomatotoxicity (78).

Several clinical observations showed the potential beneficial role of beta-carotene and some hematopoietic cytokines in the maintenance of mucosal integrity following high dose chemotherapy. Beta-carotene is an antiproliferative agent which produces regression of leukoplakia, and in patients, who received supplemental beta-carotene, the grade of mucositis was lower (79). Systemic use of hematopoietic cytokines such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interleukin-1 and 11, and transforming growth factor β appear to affect the proliferation of mucosal cells, but mouthwashing with those agents has not been found beneficial (80-85). Even though animal studies demonstrated a beneficial role of glutamine and prostaglandin in the maintenance of mucosal integrity after chemotherapy, human trials failed to confirm these results (86,87).

Theorizing that a reduction in the number of microorganisms in the oral cavity may result in a decreased incidence and severity of oral cavity mucositis, the effect of antimicrobial rinses in prevention of mucositis have been

investigated in clinical trials. There are many trials with chlorhexidine rinses, a broad spectrum antibacterial solution, but the results of these studies are controversial (88-96). Lozenges composed of polymixin B, tobramycin, and amphotericin B provided more effective mucositis prevention in patients receiving high dose chemotherapy, but it still needs confirmation (16,97). Also the advantage of chamomile rinses in prevention of mucositis remains still controversial (26,98). Even though the effect of antiseptic-antiinflammatory agents are not clear, in general, prophylaxis of oral mucositis is mainly based on dental restoration or edentation, in combination with frequent oral hygienic measures including antiseptic mouthwashes after the meals (99).

Once mucositis has occurred, treatment consists of measures to palliate symptoms (99). Debridement of necrotic tissue is very important. Cleaning the oral hard and soft tissues may be done with a 4x4 inch gauze pad wrapped around a finger or with a disposable sponge moistened in a mild solution of baking soda and water. Patients should be encouraged to use warm baking soda rinses several times a day for ulcerated and painful oral tissues (16,18,26,100). Every cancer center has adopted different available formulated solutions for the treatment of oral ulcerations: Kaopectate, diphenhydramine, lidocaine, oral antacids and commercial mouth rinses. It should be kept in mind that after mucositis occur, antibiotic rinses such as chlorhexidine may be irritating and their efficiency on mucositis is not well known (16). Topical anesthetics or systemic analgesics are recommended for pain relief. The bioadhesive agents such as hydroxypropyl cellulose may serve as a barrier over mucosal ulcerations allowing for pain relief and improved healing (101,102). In a recent literature, clinical administration of a "Magic Mouthwash", which is a mixture of equal parts magnesium aluminum hydroxide, diphenhydramine, and viscous lidocain, and a mucosal coating agent, which is composed of nystatin, lidocain, solucortef, sucralfate, and syrup alta in suspension, have been reported (16).

At present time no agent has been shown to be uniformly efficacious and can be accepted as standard therapy, but those agents with beneficial effects may be recommended for prevention and management of oral mucositis in patients receiving chemotherapy. The results of ongoing trials and future cooperative clinical oncology group protocols will be of benefit to develop more efficient strategies.

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