Oral Complications of Cancer Therapy

The mouth is a frequent site of complications arising from drug or radiation cancer therapy, with mucositis, xerostomia, osteoradionecrosis, and local infections being the most common. From the standpoint of dose

...the mouth is a frequent site of complications associated with drug and radiation therapy for cancer,[1] and interest in these complications has increased precipitously. For example, a 40% rise in literature citations for mucositis was noted for 1996-2000 compared with 1991-1995. The increased importance of oral complications is attributable to at least four factors: First, the use of marrow-stimulating growth factors has made the management of neutropenia readily available, and has successfully reduced its impact as a dose-limiting toxicity.[2] Second, the use of increasingly aggressive single-agent or multiagent drug therapy has resulted in increased oral toxicity.[3] Third, the application of new radiation regimens, many including concomitant chemotherapy, has contributed to a marked increase in oral toxicity, such that optimal tumoricidal regimens are threatened.[4] Finally, a series of studies have demonstrated that oral complications have a significant impact on nonoral health and economic outcomes.[5,6]

Mucositis

Oral mucositis is probably the most significant oral toxicity associated with cancer treatment. Its severity is often of such a magnitude as to require parenteral narcotic intervention, reduced drug dosing, or altered radiation schedules. The prevalence of clinically significant mucositis has become an important limitation to the introduction of innovative forms of concomitant or combination drug regimens. For many cancer patients, mucositis is the most notable side effect of treatment.[7] However, the overall frequency of mucositis is dependent on a variety of patient- and regimen-related variables.

Risk Factors

Certain populations are at exceptionally high risk, including patients receiving conditioning regimens for bone marrow transplant, particularly those including total-body irradiation; patients receiving induction therapy for leukemia; and patients who are being treated with fluorouracil (5-FU) infusional therapy for colorectal cancer. Patients who receive radiation therapy for tumors of the head and neck also demonstrate a high rate of clinically significant mucositis,[8] especially if they are receiving concomitant chemotherapy.

Although the drug or radiation treatment regimen is probably the most noteworthy determinant of risk for mucositis, a number of other variables are also important.[9] The presence of local mucosal irritation secondary to faulty dental appliances or trauma, secondary infection, and xerostomia all increase the risk of mucositis. Patients with hematologic malignancies develop more severe and more frequent mucositis than do comparable patients with other types of tumors. This observation is probably attributable to the tumor-induced functional neutropenia that these individuals develop. The effect of age as a risk factor is unresolved. It appears that younger populations are at increased risk, perhaps because of a greater epithelial rate of proliferation.

Patients with poor oral hygiene tend to have more, and longer lasting mucositis than do patients with clean mouths. The initiation of aggressive oral hygiene protocols has been shown to favorably affect the course of mucositis, probably by reducing the mouth’s bacterial load. Sloan et al recently reported a female predilection for mucositis induced by 5-FU.[10] Finally, there could be genetic factors that influence the risk of mucositis. For example, because proinflammatory cytokines play a role in the pathogenesis of the condition, patients who express these proteins at high levels may be more likely to develop mucositis.

Clinical Features

Mucositis represents a clinical continuum. Mild mucositis produces mucosal erythema that is accompanied by burning or soreness similar to that experienced following a food burn. In patients
receiving radiation, the condition is usually first noted at cumulative doses of 20 Gy, after
approximately 2 weeks of treatment with conventional radiation protocols of 2 Gy/d (5 d/wk).
Mucositis worsens with accumulating radiation. By the time 30 Gy has been administered,
breakdown of the mucosal surface is apparent, manifesting as pseudomembranes, or a fibrinous
mass, overlying necrotic and ulcerated tissue. Ultimately, full-thickness mucosal ulceration develops
and may persist for approximately 2 to 4 weeks after radiation ceases.[11]
Chemotherapy-induced mucositis is more acute and is generally observed within 2 weeks of drug
administration (usually between 1 to 2 weeks). In the case of chemotherapy-induced mucositis, a
distinct erythematous stage may not be seen. Rather, after a brief, 1- or 2-day period of atrophy,
superficial sloughing, and redness, the tissue becomes ulcerated and covered by necrotic tissue. This
breakdown often precedes the nadir of neutropenia by 2 to 3 days. Ulceration persists for
approximately 1 or 2 weeks, during which neutropenic patients are most susceptible to bacteremia
and sepsis through mucosal breaks. In the absence of secondary infection, lesions resolve
spontaneously.[12]

**Health and Economic Significance**
It is becoming increasingly apparent that mucositis drives a number of health and economic
outcomes. The strong relationship between mucositis, bacteremias, and sepsis is well
established.[13] Similarly, the trend toward an increasing frequency of viridans streptococcal
infections in myeloablated patients is largely attributable to mucositis; the presence of mucositis
confers a three- to fourfold greater probability of viridans streptococcal infection.[14] Thus, the
finding that mucositis is associated with increased use of health resources is not surprising. Reuscher
et al found that among autologous bone marrow transplant recipients, mucositis was associated with
a significant increase in the length of hospital stay.[15]

In one recent study of hematopoietic stem-cell transplant recipients, Sonis, Oster, and colleagues
explored the relationship between mucositis and selected clinical and economic outcomes.[6] They
found that the extent and severity of mucositis significantly contributed to the use of analgesics,
total parenteral nutrition, injectable antibiotics, and to the risk of significant infection, prolonged
hospital stay, and increased hospital charges. In the cohort studied, severe ulcerative mucositis
resulted in hospital charges that were $43,000 greater than those for patients without the condition.

**Biological Factors**
The pathogenesis of mucositis is more complex than was first envisioned.[16] Challenge to mucosal
tissue with stomatotoxic forms and doses of chemotherapy or radiation initiates a parallel and
sequential series of events that result in injury. The generation of oxygen-free radicals and DNA
damage are primary events in the process, triggering a variety of signal pathways that result in
downstream events.

Although mucositis is generally considered an epithelial process, electron microscopic evidence
suggests that early changes occur in both the endothelium of submucosal blood vessels and
connective tissue. The nature of these changes is currently being defined, but they may stimulate
additional molecular activity. For example, it seems probable that damage to connective tissue leads
to a disruption of fibronectin. This breakup can result in stimulation of proinflammatory cytokines
and production of potentially destructive metalloproteinases.

**Up-regulated Genes**
It appears that a number of genes in mucosal tissue are up-regulated almost immediately following
exposure to radiation. Many of these genes, such as p53, are associated with the response of
epithelial cells to injury. Others reflect an almost immediate attempt by the tissue to initiate healing.
Of particular interest is the finding that genes controlling certain proinflammatory cytokines—in
particular, tumor necrosis factor (TNF)-alpha and interleukin (IL)-6—are up-regulated at a rate that
parallels the development of mucositis.[17] In contrast, no increase in the expression of genes for
transforming growth factor (TGF)-beta or IL-2 has been demonstrated. Like TNF, submucosal cellular
expression of IL-1β also increases during, and correlates with, the development of mucositis.[17] A
correlation between plasma levels of TNF-alpha and IL-6 and the severity of mucositis has been
reported.[18]

**Oral Environment**
It also seems that the local oral environment and, in particular, the oral microbiota and saliva
influence the course and severity of mucositis.[19] The mouth’s microflora consists of bacteria, fungi,
and viruses. The bacterial load of the mouth is among the greatest of any site in the body.
Consequently, breaks in mucosal integrity caused by mucositis serve as a conduit for systemic
influxes of bacteria, especially in neutropenic patients. Although the predominant bacteria in the
mouths of healthy individuals are gram-positive streptococci, an increase in gram-negative
organisms occurs during periods of myelosuppression. During the 1970s, the frequency and sequelae of gram-negative sepsis led to the development and prophylactic use of quinolone antibiotics.[20] The advent of these agents reduced the incidence of gram-negative infections but caused an increase in gram-positive infections, many of which were derived from the mouth. In addition to causing bacteremias and sepsis, the bacteria that secondarily colonize ulcerative lesions of mucositis spew out cell wall products and endotoxins into the underlying submucosa. These materials serve to amplify the production of proinflammatory cytokines with the consequence of producing worsening lesions of increased duration.[21] Thus, one intervention strategy has been directed at lowering the local bacterial load.

**Xerostomia**

Xerostomia appears to predispose for the development of mucositis.[22] Desiccated tissue is more likely to break down than normal, moist mucosa. In addition, saliva plays an important role in controlling the level of local bacteria. Not only does saliva perform a washing function to clear microorganisms, but it is also rich in bactericidal enzymes and immunoglobulin A (IgA). The latter binds to bacteria and prevents their adherence to tissue.

**Approaches to Treatment and Prevention**

There is no effective approved treatment for mucositis. Approaches to the prevention and treatment of mucositis have included the use of palliative, cytoprotective, anti-inflammatory, and antimicrobial agents, and cytokines.[23] Palliation is the most commonly used approach. Traditionally, saline and bicarbonate rinses have been used to palliate symptoms. Sucralfate suspensions have been used to coat ulcerative areas with the goal of reducing pain and enhancing healing. However, trials of sucralfate have had mixed results.[24,25] Viscous lidocaine, dyclonine (Dyclone), diphenhydramine, and loperamide may provide temporary topical analgesia, but, in general, topical palliation is ineffective for patients with significant ulcerative lesions. Pain management has been best achieved with parenteral narcotics.

Several cytoprotective agents have been evaluated with mixed and often conflicting results. Cryotherapy with ice chips seems to be marginally beneficial in patients being treated with 5-FU.[26] Allopurinol, once thought to have efficacy, did not prove effective when tested clinically in patients being treated with 5-FU. Glutamine rinses have been evaluated extensively as an intervention for chemotherapy-induced mucositis, but have produced mixed results.[27]

**Pentoxifylline**

Pentoxifylline appeared to hold promise for the treatment of mucositis. A xanthine, pentoxifylline was shown to attenuate the production of proinflammatory cytokines, particularly TNF-alpha through inhibition of TNF messenger RNA transcription.[28] Additionally, it inhibits cellular phosphodiesterase and increases levels of cyclic AMP, thus conferring its effect on vascular endothelium. Consequently, from a mechanistic standpoint, it seemed an excellent candidate for treating mucositis.

Unfortunately, the results of clinical studies among patients receiving stomatotoxic chemotherapy have produced inconsistent results.[29,30] This lack of agreement among studies is illustrative of the potential pitfalls of mucositis trials. Variations in patient populations with respect to tumor diagnosis, therapy, scales used to measure mucositis, outcomes, and controls all act to confound interstudy comparisons.

As noted, the generation of free radicals is a common precursor to mucosal injury. To date, inconsistent results have been noted with the use of antioxidant or free-radical scavenger therapy agents such as vitamin E,[31] beta-carotene,[32] azelastine (Astelin),[33] and amifostine (Ethyol).[34] The role of prostaglandins in the genesis of mucositis has not been defined. Thus, whether they are beneficial or detrimental in the pathogenesis of mucositis is unknown. Nonetheless, clinical studies of inhibitors of prostaglandin synthesis, prostaglandins, and prostaglandin analogs (eg, misoprostol [Cytotec]) have been conducted, with contradictory results.[35-38]

**Anti-inflammatory Agents**

Inflammatory changes characterize the early clinical course of mucositis, particularly that induced by radiation. Consequently, a number of anti-inflammatory agents have been evaluated. Benzydamine (Tantum), a nonsteroidal anti-inflammatory agent used as a topical solution, is an effective TNF-alpha suppressor[39] with a variety of other actions that might affect mucositis.[40] The results of trials in patients undergoing radiation therapy suggest its potential efficacy.[41] Steroids are a common component of many institutionally developed mouth rinses, but data supporting their use are limited. Indomethacin was ineffective in modulating radiation-induced muco-sitis,[35] and the success of IV immunoglobulin in the treatment of several blistering mucosal diseases, such as pemphigoid, was not duplicated for mucositis.[42]

**Mucosal Decontamination**
Because it appears that a reduction in the mouth’s heavy bacterial load favorably affects the course of mucositis, mucosal decontamination is another possible treatment strategy. Chlorhexidine gluconate appears to be of equivocal value when used in patients receiving chemotherapy, and of no benefit (and perhaps deleterious) in patients receiving head and neck irradiation.[43] Like chlorhexidine, povidone iodine was originally developed as a surgical scrub. It appears to have potential activity as a mucosal decontaminant when used as an oral rinse.[44] Spijkervet and colleagues combined three agents—polymyxin E, tobramycin, and amphotericin B—and found that when used in lozenge form, they were effective in reducing the severity of radiation-induced mucositis.[45] Other studies of this approach have not been as successful.[46] Preliminary studies of the protegrin IB-367, a naturally occurring antimicrobial peptide, have produced encouraging results in patients receiving myeloablative conditioning regimens for bone marrow transplant.[47]

**Cytokine Therapy**

There has been considerable interest in the potential of cytokine therapy as an intervention for mucositis. Keratinocyte growth factor, a member of the fibroblast growth factor superfamily, has marked specificity for epithelial cells. Administration of keratinocyte growth factor results in trophic effects, characterized by thickening of the mucosal surfaces of the gastrointestinal tract. The results of studies in animals treated with radiation or chemotherapy suggest that this cytokine may be effective in preventing and treating mucositis.[48] Early trials in patients receiving stomatotoxic conditioning regimens for peripheral blood progenitor cell transplant[49] and in patients being treated for colorectal cancer have produced favorable results.

It has been hypothesized that administration of a cytokine that temporarily inhibits epithelial proliferation during exposure to chemotherapy or radiation might confer mucosal resistance. Transforming growth factor-beta 3 is such a cytokine. Animal studies with one topical formulation of TGF-beta 3 produced favorable results.[50] Although the results of a small phase I trial suggested that the cytokine was well tolerated, no conclusions could be drawn in regard to its efficacy.[51] Interleukin-11 is a pleiotropic cytokine that was originally developed because of its thrombopoietic activity.[52] However, IL-11 is also effective in down-regulating proinflammatory mediators such as TNF-alpha, IL-1-beta, and nitric oxide.[53] Results of animal studies suggest that subcutaneous injection of IL-11 favorably affects the course of mucositis induced by chemotherapy or radiation.[54]

**Colony-Stimulating Factors**

Early reports that granulocyte colony-stimulating factor (G-CSF [Neupogen]) favorably affected mucositis have not been repeated.[55] Some trials of granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine]) have reported encouraging results,[56] but others have failed to demonstrate a benefit.[57] On a speculative note, any beneficial effects of GM-CSF on mucositis may be the result of its ability to modulate TNF-alpha activity, or its antiapoptotic effect in addition to its immunostimulatory function. That said, proof of the overall benefit of GM-CSF as therapy requires additional study.

The determination of the underlying mechanisms associated with the induction of mucositis has resulted in identification of a range of biologic targets for intervention. Innovative approaches to prevention and treatment should continue to evolve in the near future.

**Xerostomia**

Xerostomia is among the most bothersome long-term adverse effects of head and neck irradiation, and is caused by radiation’s effect on the acinar cells of the serous glands. This results in inflammation, degeneration, and fibrosis of the glandular parenchyma.[58,59] The extent of xerostomia depends on the total radiation dose to the gland. Concomitant chemotherapy may increase its severity. Patients note changes as early as 1 week after the initiation of radiation. Of the major salivary glands, the parotid is the most serous and, thus, is most affected by radiation. As the amount of serous, watery saliva is reduced, patients complain of thickened, ropey saliva. Xerostomia in patients receiving cumulative radiation doses of 60 Gy or more may be irreversible.

Saliva plays an important role in controlling the oral bacterial load, as it continually flushes the mouth, contains antibacterial enzymes, and is a rich source of IgA. A reduction in saliva increases the risk of oral infections, including dental caries, periodontal disease, and candidiasis. In addition, xerostomia affects a patient’s ability to taste, swallow, and speak.

**Prevention and Treatment**

The prevention and treatment of xerostomia and xerostomia-related sequelae should be initiated simultaneously with radiation therapy. Local stimulation of salivary function can be achieved with the
Oral Complications of Cancer Therapy

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use of sugar-free lemon drops. Pilocarpine (Salagen), a cholinergic agent, has demonstrated efficacy in stimulating salivary function.[60] However, for pilocarpine to be effective, there must be some residual glandular function present. Pilocarpine is generally administered as a 5-mg tablet three times daily. Amifostine, a free-radical scavenger, has demonstrated efficacy in patients with radiation-induced xerostomia when administered intravenously prior to each day's radiation fraction.[61] Salivary substitutes are readily available and can be used to palliate desiccated mucosa.

Because patients with radiation-induced xerostomia are at heightened risk for caries, the aggressive use of a supplemental topical fluoride should be encouraged. Fluorides are available as gels or rinses, are well tolerated by patients, and have demonstrated efficacy in reducing the rate of radiation-related caries. In addition, it is becoming increasingly clear that the risk of xerostomia can be favorably affected by the use of modified radiation techniques.[62]

Osteoradionecrosis

Osteoradionecrosis is a significant potential complication of head and neck irradiation, although it is not associated with the whole-body irradiation performed in bone marrow transplant conditioning regimens. First described in 1922, the condition results in denudation of soft tissue and exposure and necrosis of underlying bone, causing a chronic, painful, foul-smelling, festering lesion.[63] A relationship between tooth extraction, radiation, and infection has been consistently reported.[64] Current thinking is that osteoradionecrosis results from a defect in wound healing that is a consequence of diminished vascularization secondary to irradiation, and that it does not represent an infectious process.

The frequency of osteoradionecrosis is unresolved, ranging from 4% to 44%, depending on the study.[65] Overall, it appears that the risk is about 15%. The mandible is involved more often than the maxilla. The timing of osteoradionecrosis relative to the initiation of radiation therapy is controversial, with some cases being reported within 2 weeks of the first radiation dose, and the majority developing later (but within the first year). Patients with teeth are twice as likely to develop osteoradionecrosis as are edentulous patients. This is especially true of patients with preexisting dental disease. Consequently, the preradiation elimination of occult dental infection is an effective strategy for minimizing the occurrence of this complication.[66]

As with other complications of radiation therapy, the field size, dose rate, and total radiation dose have an impact on the rate at which osteoradionecrosis develops. A dose of 65 Gy or more delivered to the mandible or maxilla (as opposed to other head and neck sites) increases the risk of osteoradionecrosis in nonlinear fashion. Thus, the risk in patients receiving 80 Gy is twice that of patients receiving 55 Gy and is likely associated with the amount of the jaw included in the irradiated field.

Nutritional or immunologic compromise of the host also increases the risk of osteoradionecrosis, as does smoking during head and neck irradiation. Although imaging may help with diagnosis, in the majority of cases, clinical presentation and history are sufficient.

Treatment

Fortunately, most cases of osteoradionecrosis respond to conservative treatment consisting of long-term oral antibiotic therapy (eg, penicillin or tetracycline), local debridement, and saline irrigation.[67] Resolution generally occurs slowly. Hyperbaric oxygen appears to be useful in stubborn cases, but is not used routinely. Moreover, osteoradionecrosis is usually not considered to be a surgically treated disease, although debridement and resection do have a role in severe or refractory cases.[68]

Conclusions

Oral complications of nonsurgical cancer treatment often create a significant impediment to optimal tumoricidal regimens. The frequency and severity of these complications, particularly mucositis, have sparked a surge of investigational interest directed at understanding the mechanistic complexities leading to stomatotoxicity, and at developing therapeutic strategies to prevent or treat them.

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