Abstract Mucositis is the intensity-limiting toxicity in the management of locally advanced non-resectable head and neck cancer with radiotherapy and chemotherapy. New radiation modalities (hyperfractionation and/or acceleration) as well as combined modality regimens in this situation induce higher rates of acute toxicity. Hyperfractionation, for example, allows higher control rates, with few late toxicities, but it slightly increases acute mucositis. The addition of chemotherapy introduces systemic toxicity and can exacerbate local tissue reactions when used concurrently with radiotherapy. Mucositis is recognized as the principal limiting factor to further treatment intensification. As local regional control and overall survival are related to dose-intensity in this case, further research into the assessment, analysis, prevention and treatment of mucosal toxicity is not only crucial to improvement in quality of life, but certainly also to improved rates of disease control. Several topical and systemic treatments are directed to the decrease and the acceptance of this acute toxicity, but few have shown a significant preventive effect. The efficacy of low-level laser therapy in the management of such toxicity could hence yield important developments with this method in the field of oncology.

Keywords Mucositis · Stomatitis · Chemotherapy · Radiotherapy · Head and neck cancer · Low-level laser therapy

Introduction

Despite significant survival improvement in patients with unresectable head and neck squamous cell carcinoma due to aggressive radiochemotherapy regimens, survival remains rather poor in this situation, with a 3-year overall survival of around 50%. Moreover, radiochemotherapy regimens induce high levels of acute toxicity, significantly higher than for radiotherapy alone. Indeed, 80% of patients treated with radiochemotherapy have grade III or IV hematological toxicities, 60% have grade III or IV mucositis, 20% have grade III or IV dermatitis, and 5% of patients die during concomitant chemoradiotherapy [1, 8, 9, 19, 34, 40, 47]. Virtually all patients who receive radiotherapy and/or chemotherapy for their head and neck cancer develop oral complications [7, 13, 20, 21, 23, 24, 25, 32, 42, 43, 44].

Mucositis is not only painful but can also limit adequate nutritional intake and decrease patients’ willingness to continue treatment. Severe mucositis with extensive ulceration may necessitate costly hospitalization, enteral or parenteral nutrition, and use of narcotics [3, 4, 36, 37, 38]. Mucositis diminishes the quality of life and may result in serious clinical complications [35]. A healthy oral mucosa serves to clear microorganisms and provides a chemical barrier that limits penetration of many compounds into the epithelium [6]. A mucosal surface that is damaged increases the risk of a secondary infection and may even prove to be a nidus for systemic infection. Mucositis may necessitate interruption of chemotherapy cycles or radiation therapy, which ultimately may compromise the locoregional response. An optimal management of mucositis that results in optimal maintenance of dose-intensity (both for chemotherapy and radiotherapy) could hence influence locoregional control and survival in many cases [16, 26, 27]. Investigations of altered fractionation in radiotherapy are associated with “acceptable” but somewhat increased acute toxicity, mucositis being the main limiting factor. The use of induction chemotherapy, and then of combined modality concomitant regimens, introduced the
morbidity of cytotoxic drugs (mucositis being also an important part of this morbidity), but these regimens were accepted on the promise of improved results [33, 46, 59, 61]. The use of aggressive supportive care has resulted in drifting definitions of what is considered an “acceptable” level of toxicity. Meanwhile, several trials of accelerated fractionation have produced unacceptable levels of mucosal damage, indicating that there is a limit to the ability of mucosa to recover from cytotoxic insult. This suggests that for many aggressive treatment programs mucositis is the dose-limiting (or intensity-limiting) toxicity [33]. Further increases in treatment intensity will require a better understanding of the pathophysiology of mucositis and the development of active pharmacologic modifiers of this toxicity [54, 55].

**Definition: what is mucositis?**

Pathologic evaluation of mucositis reveals a shallow ulcer thought to be caused by depletion of the epithelial basal layer, with subsequent denudation. The wound-healing response to this injury is characterized by inflammatory cell infiltration, interstitial exudate, fibrin and cell debris, producing a “pseudomembrane” analogous to the eschar of a superficial skin wound. When hydrated by saliva, this membrane appears white or opalescent. Superficial infection can make it appear yellow or even greenish, especially if deep ulceration is present [50]. The color can also be altered by food, drink, or topical medication. While the lesion represents an ulcer, close inspection often reveals the membrane to be slightly raised above the plane of the surrounding mucosa. It can be easily confused with *Candida* infection. Indeed, a mixed picture can be present with superinfection of the ulcer by *Candida* [52]. The membrane can be dislodged by minor trauma causing bleeding and further ulceration.

As the ulcer enlarges, it geographically connects to adjacent ulcers, producing a larger “confluent” pseudomembrane. In radiotherapy, the reaction is confined to the treatment portal. The edge of the portal can often be visualized on the mucosa as a rim of intense erythema (Fig. 1). Ulcers from chemotherapy are histologically similar but generally remain in a “patchy” phase. They occur throughout the aero-digestive tract but are usually only appreciated in the anterior oral cavity (Fig. 2). Regeneration of the stem cell compartment eventually results in re-epithelialization and resolution of the ulcer. Superinfection by yeast, bacteria, or viruses may contribute to delayed healing. Larger deep ulcers often require prolonged healing times. Profound depletion of the stem cell population may result in healing by secondary intention by granulation tissue/scar. Depending on the extent of the injury, the resulting mucosa may appear pale, atrophic, and less compliant. Some deep ulcers never appear to heal and these progress to soft tissue or bone necrosis. While systematic clinical studies of these pathologic changes have not been performed in humans, deep ulceration requiring prolonged healing probably produces what are clinically noted as “consequential” late effects in the mucosa.

For high-grade (III/IV) reactions, the “peak” or maximal observed mucositis is only partially indicative of the degree of stem cell depletion. The duration of injury also reflects the magnitude of depletion and rate of recovery.

**Causes of mucositis**

(1) Direct stomatotoxicity

Normally, cells of the mouth undergo rapid renewal over a 7–14-day cycle. Both chemotherapy and radiotherapy interfere with cellular mitosis and reduce the regenerative ability of the oral mucosa. Cancer chemotherapeutic drugs that produce direct stomatotoxicity include antimetabolites, alkylating agents, natural products, and other synthetic agents such as hydroxyurea and procarbazine hydrochlo-