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Review

Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature

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ABSTRACT

Oropharyngeal mucositis is an important complication in non-surgical cancer treatments. It represents the major complication in radiotherapy of tumors located in head and neck areas. Many results have been published in order to define the best clinical protocol for prophylaxis or treatment of mucositis, but a consensus has not been attained yet. In this review, some recent topics in prophylaxis and treatment of mucositis related to radiation therapy are reconsidered using PUBMED and GOOGLE SCHOLAR search engines from 2000 to 2015. In this review, more than 100 clinical studies have been selected and divided into the prophylactic or therapeutic uses of the evaluated treatment agents. The number of patients and kind of study design, the clinical features, prevalence, risk factors, pathogenesis, diagnosis, complication, prophylaxis and the treatment of mucositis were also specified. Nevertheless, it has not been truly achieved a consensus protocol of prophylaxis and treatment of oral mucositis.

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Radiation therapy plays an important role in the treatment of patients with head and neck cancer. Regulated by the location of the malignancy (primary tumor and lymph node metastases), necessarily, the salivary glands, oral mucosa, and jaws have to be included in the radiation treatment protocols [1]. Although, that may result in short and long term side effects, this kind of treatment is more effective than the others. Possible side effects include: mucositis, osteoradionecrosis, taste loss, hyposalivation, radiation caries, periodontal disease, trismus and so on [2]. Among the acute clinical side effects, disruption in the function and integrity of the mouth are the most important cases. These complications can result in severe ulceration called mucositis. Recently, many studies have been published on the radiation-induced oropharyngeal mucositis associated with the treatment of head and neck tumors. The mucositis may be accompanied with other complications such as oral discomfort, pain, poor nutrition, delays in drug control, increased hospitalization and costs as well as life threatening infection in some patients. For all of these reasons, the oral mucositis should be prevented or minimized as much as possible [3]. In this review, some recently topics in prophylaxis and treatment of mucositis related to radiation therapy are reconsidered using PUBMED and GOOGLE SCHOLAR search engines

from 2000 to 2015. In this search, more than 100 clinical studies have been selected and divided into the prophylactic or therapeutic uses of the evaluated treatment agents. The number of patients and kind of study design, the clinical features, prevalence, risk factors, pathogenesis, diagnosis, complication, prophylaxis and the treatment of mucositis were also specified. Nevertheless, it has not been truly achieved a consensus protocol of prophylaxis and treatment of oral mucositis.

Clinical appearance

Radiation-induced mucositis is quite bothersome due to acute the complications in patients receiving radiotherapy and even more pronounced with the combined chemoradiotherapy. Mucositis manifests itself as erythema, edema or ulceration that can be accompanied by a mild burning sensation [1]. Extreme appearances are characterized by large and painful ulcers that have a large impact on patient's quality of life. It may seriously restrict simple activities such as speaking, eating or even swallowing saliva [4]. The early clinical sign of mucositis is erythema appearing at cumulative doses of head and neck radiation of about 10 Gy. At this stage, the patients also often complain of burning sensation and intolerance to spicy foods. When the cumulative reaches 30 Gy (generally after 2 weeks), ulcers develop, resulting in marked troublesome symptoms, often requiring opioid consumption. In many cases patients are forced to alter their life style [5].

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Radiation-induced mucositis may involve any radiation-exposed area, including the hard palate, lip, buccal mucosa, tongue ventrolateral aspect and base of mouth [2] (Fig. 1). It remains at its peak for at least 2 weeks following the completion of radiotherapy (commonly 60–70 Gy). After that, symptoms of oral mucositis can then persist for up to 8 weeks. Chronic mucositis following the completion of radiation-therapy is rarely seen. Healing begins soon after the completion of the treatment [6].

Prevalence

In general, oropharyngeal mucositis occurs in more than %90 of patients who receive radiation and or chemotherapy for head and neck tumors [7]. It occurs in almost all the patients who are treated for cancers of the mouth, oropharynx, nasopharynx, and in approximately two-thirds of those treated for cancers of the hypo pharynx or larynx [8]. Hagiwara et-al reported that %80 of patients undergoing radiation-therapy showed oropharyngeal mucositis and %29 developed severe oropharyngeal mucositis [9]. Patients with severe oropharyngeal mucositis are those with nasopharyngeal or oropharyngeal tumors. Patients with oropharyngeal mucositis had more unplanned interruptions in their radiation/chemo-therapy schedules and hospital admissions than other tumor sites with oral mucositis [8].

Risk factors

The risk factors depend on the patient, such as the location of the tumor (e.g. hematological diseases), age (e.g. young patients), oral and dental hygiene, the nutritional condition of the patient, and the maintenance of liver and kidney function [10]. Other risk factors are related to the ionizing radiation such as the dose, fraction size, radiation portals, fractionation, and the type of the ionizing irradiation.

Pathophysiology

The pathogenesis of oral mucositis is not completely understood, but it is known that it involves direct and indirect

mechanisms. The direct mechanisms of irradiation include interrupting the cell renewal cycle and apoptosis. The indirect mechanisms leading to oral mucositis include the release of inflammation mediators, the loss of protective salivary role and neutropenia induced by the treatment [10]. These factors may increase the probability of the manifestation of bacterial, viral and fungal infections on the injured mucosa. Recent studies have indicated that the mechanisms involved in the pathogenesis of oral mucositis are much more complex than a direct damage to the epithelium alone. The progression of oral mucositis classifies to five stages and some cytokines are responsible for the stages [11] (Fig. 2).

WHO has developed a grading scale for assessing oral mucositis based on the clinical appearance and also the functional status. The scale depends on both objective and subjective variables, and anatomical measures, symptomatic and functional components of oral mucositis [12] (Fig. 3).

Diagnosis

Oral mucositis is typically diagnosed based on the clinical feature, location, timing of oral lesions, and the use of certain other causative types of therapies. Some scales are available, including those developed by WHO [13] (Supplementary file 1), the Radiation Therapy Oncology Group, Western Consortium for Cancer Nursing Research, and National Cancer Institute (NCI), among others. WHO oral toxicity scale and the NCI common toxicity criteria are the two most commonly used scales for oral mucositis.

The radiotherapy technique

Oral mucositis is defined as an inflammation of oral mucosa followed by an ionizing radiation. The severity of radiation-induced oral mucositis is strongly dependent on the dose, fraction size, radiation portals, fractionation, and the type of the ionizing radiation used [14]. The use of various radiation treatment protocols and schedules of fractionation can play an important role in the prevention of mucositis [12]. The use of high-energy photon beams, with linear accelerators, present a more homogenous dose distribution in and outside of the target area compared to the older and mostly outdated orthovoltage technique. This is



Fig. 1. Various parts of oral cavity affected by radiation-induced mucositis.

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