Oral Mucositis Induced by Chemoradiotherapy

Subjects: Oncology

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Oral mucositis, a severe non-hematological complication, can be induced by chemoradiotherapy. It is associated with severe local dysfunction, severely affecting the patient's quality of life; it increases the risk of oral infections and interrupts oncological treatment, thus prolonging the duration and cost of hospitalization.

oral mucositis honey head and neck cancer chemotherapy

1. Introduction

Currently epidemiological data support that head and neck tumors are a public health problem due to their increasing incidence, prevalence and high mortality. Head and neck cancer (HNC) accounts for more than 550,000 cases and 380,000 deaths annually, worldwide [1].

Head and neck oncology faces real challenges as these types of tumors have serious repercussions on the patient's quality of life. They affect various areas that directly interfere with the patient's everyday life, such as: speech, taste, ability to chew, swallow, breathe, facial bone changes, dental mobility, local or remote vascular-nerve functionality, physical appearance; these types of cancers can also have a profound, long-lasting psychological impact, sometimes with extensive recovery processes. Therefore the treatment of Ear, Nose & Throat (ENT) cancers is extremely complex, multimodal and requires, on one hand, the involvement of a multidisciplinary therapeutic team, which must include medical oncologists, radiation therapists, pathologists, dentists, nutritionists, and on the other hand, the availability of certain technologies and techniques for radiotherapy (3D conformal 3DCRT or intensity modulated, IMRT). In addition to surgery and radiotherapy, chemotherapy and immunotherapy have undergone major developments, based on new and effective clinical trials but with more or less manageable toxicities [2][3].

Of all chemoradiotherapeutic toxicities, OM seems to be difficult to manage and despite many studies, there is no unanimously accepted protocol by clinicians today [4].

Considered one of the most severe non-hematological complications, OM seriously affects the patient's quality of life. It is associated with severe local dysfunctions, increases the risk of oral infections, may interfere with oncological treatment prolonging the duration and cost of hospitalization [5].

From a radiobiological point of view, the oral mucosa is one of the acute-response tissues whose lesions may be reversible and frequently occur during irradiation or after treatment completion [6].

However, radiotherapy has an adverse influence on other mucosae and the inflammatory and indurated cutaneous changes associated with mucositis (as an expression of the effects of radiotherapy) must be clinically dissociated from other dermatological manifestations, similar in clinical expression: atrophic lichen sclerosus, morphea or lichen planus [7].

In order to prevent and treat chemoradiotherapy-induced OM, a variety of natural and synthetic substances are currently used. In addition to the recognized and marketed recommendations, more and more emphasis is being placed on natural products in view of their minimal adverse effects [4].

One of the best known natural agents is honey, which can be defined as a heterogeneous mixture of substances such as proteins, sugars, which come from the nectar of flowers and glandular secretions produced by bees. Honey is an extremely complex product and can be considered both a plant and an animal product [8][9]. Honey contains more than 200 different natural compounds, grouped into macro and micronutrients, depending on the type of bees, natural floral source, environmental factors and processing methods. Among the compounds that make up honey are: sugar, proteins, enzymes, minerals, vitamins, amino acids and a wide range of polyphenols. These compounds give honey its color, taste, viscosity and various therapeutic properties. Various scientific studies have shown that honey has numerous benefits. Thanks to flavonides and phenolic acids, honey has important antimicrobial activity. Moreover, it has antiviral, antioxidant, anti-inflammatory and antineoplastic effects [10]. These properties can be attributed to physicochemical characteristics such as high osmolarity and low pH, due to the presence of organic acids; the concomitant effects of the antioxidant and antimicrobial properties of honey, together with the anti-inflammatory properties, produce a healing effect on lesions. Honey is a good preventive agent against bacterial effects because its physicochemical properties provide an environment that is not conducive to bacterial proliferation, thus inhibiting the inflammation process [11].

As it can be seen, honey, as a natural agent has a broad-spectrum activity comparable to other systemic anti-inflammatory agents, e.g., dexamethasone, which due to its anti-inflammatory and other effects can be used in dermatology, oncology, surgery, etc. [12]. Honey also stimulates the immune system by producing antibodies [13]. Research has established that honey has a strong impact on the proliferation of B and T lymphocytes, thereby activating macrophages.

2. Oral Mucositis Induced by Chemoradiotherapy in Head and Neck Cancer

Currently, chemoradiotherapy-induced OM benefits from a multitude of pharmacological and non-pharmacological therapeutic options. Although numerous agents exposed in the researcher's research are available, researchers have not yet reached a consensus regarding the prevention and treatment of this toxicity [14]. There are many studies in the literature on the usefulness of honey in the prevention and treatment of OM based on the biological

properties of this agent. As an anti-inflammatory and antimicrobial agent and immunomodulator, this natural product has a great impact on OM [8][9][10][11][13][15][16]. For example, Pradip Kumar Maiti et al. conducted a study on 50 patients diagnosed with head and neck cancer who were radiotreated and divided into two study groups. The study arm was given 20 mL of honey 15 min before, 15 min after treatment, and a similar amount at bedtime. After evaluation, there was a significant reduction in grade 3 or 4 OM in the honey arm from 18% to 41% in the control arm [17]. The working method is similar to Howdler et al.'s. Both Pradip Kumar Maiti et al. and Howdler conclude that honey is an inexpensive, readily available, effective agent for treating OM. The difference between these studies is in the oncological treatment applied to the patients, i.e., radiotherapy alone versus radiochemotherapy in combination with cisplatin-based chemotherapy. Not all studies specify the type of honey used. Howdler et al. used 20 mg of fresh, organic, unprocessed honey and in the study by Pradip Kumar Maiti et al. honey of unspecified origin was used but the recommendations of the studies are similar [17][18]. On the other hand, Motallebnejad M et al. conducted a double-blind randomized clinical trial in which 40 patients randomly assigned to two groups are examined. The study protocol is similar to the studies described above. However, the type of honey used is specified, this being pure natural honey obtained mainly from Thymus and Astragale in the Alborz Mountains, northern Iran. It is assumed that the beneficial effect of honey is based not only on its antibacterial properties but also on its geographical location, pollen source, season, type of bee, or other factors influencing its quality [10][11][19]. In contrast in the subspecialty review of Tharakan, T et al. [20], in which oncology patients are administered thyme honey, polyfloral honey, Ziziphus honey, pure or diluted honey oral rinse with satisfactory results, Karsten Münstedt [21] evaluated the efficacy of conventional bee honey and Manuka honey on radiochemotherapy-induced OM. Conventional honey has been shown to be more beneficial than Manuka honey, which requires caution when administered [11] for example due to adverse effects (severe nausea, vomiting, and severe burning sensations in the mouth) it was necessary to change the protocol in a study conducted by Parsonset et al. [11][19][22]. On the other hand, Hunter et al.'s study also found adverse effects of Manuka honey in a group treated with this type of honey [11] compared to Bardy et al., who conducted a double-blind, placebo-controlled, randomized trial with 131 patients. Consequently, a different form of honey presentation is recommended using a more liquid formula with active ingredients [11][23]. In other respects in the systematic reviews and meta-analyses [24][25][26][27] introduced, reference is made to honey combined locally and systemically, "natural" honey, royal jelly, honey extracted from Camellia sinensis, Thymus, and Astragale, from the Western Ghats forests, from Trifolium alexandrenum, pure natural honey, manuka, local honey, or unspecified honey applied locally or administered systemically. The results of studies are positive, honey administered either in dilution or in pure form has beneficial effects on OM [20][28][29]. Although the literature, as researchers have extensively exposed by researchers, supports the benefits of bee honey in preventing and treating OM in patients with head and neck cancer, this topic is still controversial. Effective management of this toxicity is needed, but in neoplastic patients who are given different types of treatments such as pain relievers and anti-inflammatory drugs, which may influence the results of the research, these studies sometimes seem inconsistent [26]. On the other hand, it is very difficult to control the purity of honey, as it differs depending on a multitude of factors. In order to avoid inconsistent results in future research, it is necessary to specify and recognize the differences between different types of honey or to identify the active substances of this agent responsible for its beneficial effect on OM [21]. Despite these pros and cons, there is sufficient evidence and

scientific studies conducted by researchers recommending bee honey to be included in the guidelines responsible for the management of this post-radiochemotherapy toxicity [24][25][30][31][32].

Despite its many benefits, honey consumption is still limited. Many researchers also warn patients about potential health problems caused by the excessive consumption of honey. Although honey has extraordinary anti-inflammatory, antibacterial, antiviral, anticancer, and tissue-repairing properties, caution is still required in its consumption [16]. Moreover, honey is a food subject to adulteration. In its composition there must not be any other ingredient, flavor, or foreign substance. Honey must not be overheated in order not to lose its properties. Pure honey can be altered either directly by adding adulterants, indirectly by feeding bees, or by mixing honey with other low-quality products [33]. Apart from the nutrients and compounds that give it these beneficial physicochemical properties, there may be contaminants in the composition of honey, such as pesticides, antibiotics, heavy metals, or other toxic agents, caused by exposure to the environment, faulty handling by beekeepers, or even the presence of numerous bee diseases that can ultimately affect the quality of honey. Honey can be contaminated by various chemicals or pathogens, which is why it is recommended that before consumption honey should be sterilized in order to remove contaminated agents without losing the therapeutic properties of honey. The use of honey should not be recommended for cancer patients with associated diabetes.

Another important problem is the presence of allergens that can cause severe anaphylactic reactions. Honey can also be a factor in the development of dental caries, therefore careful care of the oral cavity is recommended, especially during antineoplastic treatment.

Given the benefits but also the contraindications, manufacturers are encouraged to label each beekeeping product appropriately, especially honey [16].

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