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ADVERSE EFFECTS IN THE ORO-MAXILLO-FACIAL TERITORY CAUSED BY CHEMOTHERAPEUTICS USED IN THE TREATMENT OF ONCOLOGICAL PATIENTS. REVIEW.

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Abstract: Chemotherapy presents a wide variety of side effects alongside the desired antineoplasic, affecting the entire organism through direct and indirect pathways. Both of these are due to the known effect of chemotherapy agents on cells with a high turn-over rate like marrow cells, mucosal cells, hair follicles. In the oral cavity the side effects that occur are due to both the immunosuppression and direct affection of mucosal cells that line the entire oral cavity. The aim of this review is to offer an update on the data present in literature regarding the side effects of chemotherapy within the oral cavity.

Keywords: *chemotherapy, oncology, side effects, adverse effects, oral manifestations. mucositis,*

Introduction

It is estimated that 15% up to 40% of chemotherapy patients will develop oral lesions during treatment according to some authors, some citing a percentage of up to 60% [1]. These modifications occur due to the direct effect of chemotherapy on oral tissues but can be overlapping on the indirect immunosuppressive effects that chemotherapy induces because of the marrow cells modifications. Thus it is possible that oral manifestations appear as a result of a combination of direct and indirect effects of chemotherapy [2].

The oral modifications that occur as a result of malignant afflictions, with or without treatment and other comorbidity factors, can have a profound effect on the patient diagnosed with cancer: pain, discomfort, gradual loss of nutrition intake and its various degrees of influence. In the long term, patients requite prolonged hospitalization that may sometimes be complicated with septicemia and exitus [3].

Review of literature

Chemotherapy can often have a negative influence on mucosal tissues because of its effects on all weakly differentiated cells or cells with a high mitotic rate. The effect of chemotherapy is toxic in a direct manner and, in some cases, the administered drug is secreted in saliva which in turn leads to alterations within the oral cavity [4,5]. Moreover, chemotherapy can affect other tissues like bone marrow which leads to a lowering of

the immune system. A low immunity status allows for a series of other problems to occur like a high risk of infection and oral hemorrhage [6].

An important number of chemotherapy agents have mucotoxicity. Of course, the intensity of the toxicity depends on a series of variables that influence the degree of oral tissue affection, like the type of anti-neoplasic agent, the therapeutic regime, intensity of the dose and the extent of therapy [7]. The soft tissues most frequently affected are the lips, oral mucosa, soft palate and pharynx mucosa [8].

The most frequent secondary effects of chemotherapy within the oral cavity which are due to the mucotoxicity a high number of cytostatic and cytotoxic agents have include: mucositis, bacterial, fungal or viral oral infections, dental alteration, taste modifications, hyposialia, xerostomia, tendency to hemorrhages and osteonecrosis [9-11]. Mucotoxicity is dependent not only of chemotherapy but also other side medications and even previous mucotoxic treatments administered. A prolonged or repetitive administration of lower doses of cytostatic agents have been associated with an increase of oral manifestations compared to in bolus administrations [12]. Moreover, the risk of developing mucositis is linked to the number of chemotherapy cycles and previous number of experienced mucositis exacerbations induced by chemotherapy.

Drugs that influence DNA synthesis (like S-phase specific agents such as 5-FU, methotrexate, cytarabine) have the highest and most pronounced mucotoxic effects. Köstler et al. listed a high number of anti-neoplasic agents with high mucotoxicity, among these being actinomycin D, cisplatin, 5-FU, methotrexate, chlorambucil, docetaxel, floxuridine, thioguanine, vinblastine, amsacrine, doxorubicin, bleomycin, vindesine, etoposide, mitoxantrone, cytarabine and daunorubicin [13].

Of the most frequently cited oral manifestations in oncological patients during chemotherapy is mucositis [14].

The pathology of mucositis implies a cascade of systemic and local events initiated by the administration of chemotherapy. Prior to the apparition of mucositis lesions there is an increase in pro-inflammatory cytokine levels such as TNF, IL-6 and IL-1β that seem to play an important role in the initiation of lesions [15].

It is an important fact that these cytokines can be found in tissues and in peripheral bloodstream. Locally, the initiation of mucositis lesions takes place in the submucosa, in the endothelial level rather than the epithelial level [16,17]. Mucositis is defined as an inflammatory lesion in the oral cavity or of the gastrointestinal space. These lesions often lead to discomfort that can affect the patient's ability to feed, swallow or speak [18].

Moreover, mucositis can provoke the dry mouth syndrome which, in turn, can lead to secondary infections that are most frequently fungal but can also be bacterial. Due to the fact that the inflammatory process can occur at any level of the digestive tract, chemotherapy patients present a higher risk of local and systemic infection [19]. In more severe cases of mucositis the patient is at risk of haemorrhage.

Moreover, severe cases may require prolonged hospitalization, parenteral nutrition and even the delay or cancelling of anti-neoplasic treatment [20]. The incidence of mucositis in patients with radiotherapy and chemotherapy in the head and neck region is approximately 85% even though the degree of severity differs from case to case. Mucositis is one of the main factors of limitation in chemotherapy treatment for advanced tumors of the cephalic extremity. Bone marrow transplant patients have an incidence of mucositis of 75%. Overall, an important part of scientific literature on malignant tumors with any localization and treated with high doses of anti-neoplasic drugs present a high risk of developing mucosistis (20-50%) [21].

Mucositis evolves in five stages:

- *Initiation.* Chemotherapy causes direct destruction on the DNA, the ceramide synthesis is stimulated and destruction of cell membrane and conjunctive tissue takes place alongside macrophage stimulation
- *Primary response*. Host cells go into apoptosis and pro-inflammatory cytokine modulation takes place
- *Signaling and amplification*. Prostaglandin production increases, reinitiation of reponse pathways to tissue destruction, amplification and intensification of immune response and apoptosis stimulation due to TNF- α action
- *Ulceration.* Cell death removes trophic epithelial factors, MMPs lead to the degradation of extracellular matrix which infiltrated with fluid and weakens the sub mucosa-epithelium attachment, thinning of the epithelia due to the apoptosis, reduced epithelial regeneration and opportunistic infections stimulate the inflammatory response
- *Healing*. The activation of cycloxagenase-2 promotes angiogenesis, the macrophages reduce the inflammatory response, epithelial cells multiply and migrate to close the gap of the ulceration, sub mucosal cells regenerate [22].

The decrease of immunity due to chemotherapy and an increase in risk of infection can cause stomato-toxicity and are the main reasons for the occurrence of mucositis. There are other factors that can have an influence in this sense like chemotherapy dosage, the extent of treatment and type of malignant tumor [23] which accumulate with factors like level of oral hygiene and intrinsic conditions of the patient.

Because mucositis is a plurifactorial pathology, it is important to understand how different clinical and treatment related variables can lead to not only the occurrence of mucositis, but also the extent of its severity and length of time during which it is present in the oral cavity [24].

Another side effect of chemotherapy is **caries lesions**. Even though the post-therapeutic incidence of dental caries is more frequently associated with radiotherapy, these may occur during or after chemotherapy as well. The process of developing caries during chemotherapy is not entirely clarified presently, but their occurrence may be linked to frequent use

of oral rinses containing sugars used to treat dry mouth syndrome [25].

The **alteration of salivary function** that appears due to administration of chemotherapy agents has an important effect on oral health status. The modulation of the entire oral cavity relies on the quantity and quality of saliva secretion. In this sense, the salivary immunoglobulins have the role of protecting the soft tissues of the mucosa from trauma and bacterial infections.

On the other hand, the tissue alterations that occur during chemotherapy increase the susceptibility to infection by generating ulcerations and profoundly perturbing the tissue regeneration processes so that even opportunistic bacterial infections can cause inflammatory processes. Also, the decrease of IgG and IgA quantities has been associated with the development of mucositis femonema [26].

The value decrease of saliva pH that occurs due to chemotherapy reduces the buffer role of saliva in the oral cavity [27] that translates into an increased risk of caries and periodontal disease.

Xerostomia is defined by a drastic reduction of salivary flux and represents one of the most frequent side effects of systemically administered chemotherapy. The symptoms associated with xerostomia are driness of mucosas, burning sensations or discomfort in the oral cavity, cracked aspect of lips, surface modifications of the tongue and difficulties related to the wearing of removable prosthetics and fluid intake [28, 29].

Oral modifications related to xerostomia can be a factor in the altering of taste that can also develop consecutive to anti-cancer treatment administration.

One of the most frequent forms of periodontal disease during chemotherapy is **necrotizing-ulcerative gingivitis** that occurs more often in patients which had periodontal disease prior to the administration of chemotherapy. Necrotizing-ulcerative gingivitis is accompanied in some cases with general status modifications like fever and adenopathy that often complicate the anti-tumoral treatment [30-33].

Conclusions

Chemotherapy causes a wide range of oral side effects alongside the systemic modifications that lead to a lower quality of life for the oncology patient and increases the risk of complications both in the oral cavity and systemically. The severity of adverse effects is sometimes as great as to interfere with the correct sequence of cytotoxic or cytostatic treatment, thus interfering with its rates of success. More care should be directed towards prevention of oral cavity afflictions prior to the start of the chemotherapy treatment and the treatment plans for oncology patients should be established through inter-disciplinary collaborations between oncologists and dentists.

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