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MUCOSITIS INDUCED BY CHEMOTHERAPY: PATHOPHYSIOLOGY AND STRATEGIES TO IMPROVE INTESTINAL RESISTANCE

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Abstract: Goal: To identify the relationship between the onset of intestinal mucositis in cancer patients undergoing chemotherapy and the influence of the degree of immunosuppression. **Methodology:** Literature review conducted through searches in the PubMed database, in which 286 articles were found and selected, after the of inclusion, 11 studies to compose. **Discussion:** Intestinal mucositis induced by chemotherapy is a major difficulty faced by patients who use chemotherapy, manifesting itself in 40% of patients with a standard dose of the drug and in 100% of patients undergoing high doses. It is noted that the occurrence of intestinal mucositis is also influenced by the age of the patients, the presence of underlying comorbidities and the type of chemotherapy used. Final Considerations: The most related drugs are methotrexate, cisplatin, irinotecan (CPT-11), oxaliplatin, irinotecan and 5-FU. In addition, there is a higher prevalence in patients of advanced age who have diabetes or autoimmune diseases. Such factors can compromise adherence to treatment and lead to a drastic reduction in the quality of life of patients.
Keywords: Intestinal Mucositis; Antineoplastics; Chemotherapy.

INTRODUCTION

Cancer is a condition that affects public health, and its prevalence is increasing worldwide. According to research, in 2020, cancer led to approximately 19,290,000 new cases and 9,960,000 deaths (WEI L. et al., 2021; CHEN X. et al., 2021). The main antineoplastic treatments consist of chemotherapy, radiotherapy and surgical interventions, in addition to the current development of other types of intervention, such as targeted therapy and immunotherapy (WEI L. et al., 2021). Despite the high effectiveness in combating neoplastic cells, such chemotherapeutic

agents, due to their potent cytotoxic action, also impact on healthy cells, and commonly cause several side effects, among them, intestinal mucositis, which will be the focus of this review study. (CHEN X. et al., 2021; WEI L. et al., 2021).

Chemotherapy-induced intestinal mucositis (CIM) refers to inflammation and ulceration of the mucosa, with complex and multifactorial pathogenesis (YU Q.-Q. et al.,2022), being an adverse reaction related to the dose of chemotherapy treatment (WEI L. et al., 2021). It is noted that about 40% of patients treated with a standard dose and 100% of patients treated with a high dose develop nausea, vomiting, abdominal pain, diarrhea and malnutrition associated with intestinal mucositis. MIC presents itself in 5 phases: (1) initiation, (2) response to primary damage, (3) signaling and amplification, (4) ulceration and (5) healing and oxidative stress, with production of high levels of reactive species of oxygen (WEI L. et al., 2021; YU Q.-Q. et al., 2022). In addition, apoptosis and dysbiosis of the intestinal microbiota (IMD) are directly related to the development of IBC (YU Q.-Q. et al., 2022), and it is noted that chemotherapy aggravates intestinal mucositis, since it shapes the intestinal microbiota through toll-like receptor (TLR) signaling pathways, increasing the expression of inflammatory mediators and apoptosis of epithelial cells, in addition to decreasing cell differentiation and mucosal regeneration (WEI L. et al., 2021).

In this context, MIC leads to a decrease in the quality of life of patients, prolonged hospitalization and increased health expenses, and may also compromise adherence and tolerance to treatment. The development of a "therapeutic alliance" is important for the prevention and/or treatment of mucositis, also representing an aid in each cycle of chemotherapy (ANDERSON P. M.; LALLA R. V, 2020). In view of this, the objective of the present study is to identify the relationship between the onset of intestinal mucositis in cancer patients undergoing chemotherapy treatment and the influence of the degree of immunosuppression.

METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used for the development of the research through its guiding question: "What is the relationship between the appearance of intestinal mucositis in cancer patients undergoing chemotherapy, including the influence of the type of medication, dosage and duration on the degree of immunosuppression?". according to the parameters mentioned above, the population or problem of this research refers to cancer patients undergoing chemotherapy with variables associated with the influence of the type of medication, dosage and duration on the degree of immunosuppression characterizing the outcome related to the appearance of intestinal mucositis The searches were carried out through searches in the PubMed Central (PMC) database. The descriptors were used in combination with the Boolean term "AND": (Intestinal mucositis) AND (Antineoplastic Agents) AND (Immunosuppression). 286 articles were found, subsequently submitted to the selection criteria. ram: articles in English and Portuguese; published in the period from 2019 to 2022 and that addressed the themes proposed for this research, studies of the literature review type, animal experiments, longitudinal retrospective study, available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion

criteria. After associating the descriptors used in the searched databases, a total of 286 articles were found. Of which, they belonged to the PubMed database. After applying the inclusion and exclusion criteria, 286 articles were selected from the PubMed database, using a total of 11 studies to compose the collection.

REVIEW

One of the most common side effects of chemotherapy is intestinal mucositis (OLIVEIRA M.M.B. et al., 2021). Antineoplastic agents, despite expressing their cytotoxic effect on cancer cells, affect other healthy cells, especially those with rapid proliferation, such as the intestinal muscle cells. One of the side effects of these drugs is the aforementioned intestinal mucositis, a condition that has serious impacts on both the prognosis and life expectancy of cancer patients, who are already debilitated due to the underlying disease (CHEN X. et al., 2021; CHEN G. et al., 2021).

MIC is present in 3.6% of patients undergoing antineoplastic treatment, showing a positive linear correlation by the Spearman coefficient, that is, its frequency increases among older patients when compared to younger ones (SARAGIOTTO L. et al.,2020). When drugs come into action, they cause damage to the intestinal mucosa and submucosa through several mechanisms, which mostly lead to the production of reactive oxygen species (ROS) that potentiate such damage. Wei L. et al. (2021) also reports that the intensity of symptoms related to MIC depends directly on the chemotherapy dose, a relationship that is expressed by its manifestation in 40% of patients with standard dose of the drug and in 100% of patients undergoing high doses.

The mechanisms of pathophysiology of intestinal mucositis still have several gaps, however, it is known that intestinal dysbiosis induced by chemotherapy is one of the important factors in the development of the disease. Such dysbiosis varies according to the dose, duration of exposure to the drug, route of administration and the chemotherapy medication used (WEI L. et al., 2021). Chemotherapy drugs cause a decrease in the diversity and quantity of intestinal bacteria, through an increase in bacteria with greater pathogenic potential and gram negative bacteria, and a decrease in beneficial and gram positive bacteria, inducing an intestinal dysbiosis that alters mucosal homeostasis. Thus, chemotherapy intensifies the expression of Toll-like receptors resulting in an increase in inflammatory mediators in the mucosa, which results in a potentiation of the effects of intestinal mucositis (WEI L. et al., 2021). In addition, there are studies that report that intestinal mucositis caused by chemotherapy is also related to cell damage, formation of reactive oxygen species and increase in pro-inflammatory cytokines, such as TNF-α, IFN-γ and IL-1β (LEE J.M. et al., 2019).

The different antineoplastic agents act in different ways in the pathogenesis of intestinal mucositis. Chemotherapeutics based on 5-Fluorouracil (5-FU), in addition to presenting high rates of ROS production, modify the synthesis of RNA and DNA, inducing apoptosis and cell damage, which causes the shortening of the villi, alteration of the architecture of the crypts, edematous mucosa and infiltration of inflammatory cells, resulting in loss of mucosal integrity, making it more susceptible to bacterial colonization (OLIVEIRA M.M.B. et al., 2021). Such patients present persistent diarrhea as the predominant symptomatology(YU Q.-Q. et al.,2022).

Chemotherapeutic drugs have higher rates of ROS production are: methotrexate (MTX), cisplatin, irinotecan (CPT-11), oxaliplatin and

the aforementioned 5-FU. Its symptomatic manifestations are quite similar to each other, where MTX has higher incidences of diarrhea, nausea and reduced absorption of nutrients; cisplatin, although very efficient, causes deficiencies in the absorption and integrity of the intestinal barrier; and irinotecan (CPT-11), produces bloating, abdominal pain, diarrhea and weight loss in their patients (YU Q.-Q. et al., 2022).

A retrospective longitudinal study performed by Saragiotto L. et al. in 2020 analyzed the nutritional status and gastrointestinal changes of cancer patients undergoing chemotherapy (n=187), presenting results of nausea in 18.54%, lack of appetite in 18.31, constipation in 11.58%, diarrhea in 7.98 %, xerostomia in 7.59%, vomiting in 7.43%, dysgeusia in 4.46%, dysphagia in 3.99%, heartburn in 1.8% of patients and mucositis in 3.6% of them (SARAGIOTTO L. et al., 2020).

In general, the main symptoms related to intestinal mucositis are nausea, vomiting, abdominal pain and diarrhea, which is related to the impairment of patients' quality of life. The way in which these symptoms manifest themselves has a significant relationship with the age, ethnicity, sex and type of Cancer (CA) of the patients. Still, underlying illnesses like diabetes or autoimmune disease lead to greater vulnerability to mucositis damage. Antineoplastic drugs also affect the highly proliferative hematopoietic system, causing systemic anemia, neutropenia, and lymphocytopenia. However, despite this imbalance in the immune system, it is the local immune response in the GI tract that promotes the development of mucositis (SOUGIANNIS A. T. et al., 2021).

A relevant point to highlight is that MIC is a condition that, although common, is still a significant clinical challenge in the treatment of cancer patients (SOUGIANNIS A. T. et al., 2021). In view of the information presented, several studies have been developed in recent years with the aim of seeking new approaches to this disease. A recent research carried out with mice obtained positive results in the control of intestinal mucositis, in which, according to Fideles L.S. et al. (2020), rutin, a natural flavonoid extracted from Dimorphandra gardneriana, a plant abundant in the Brazilian northeast biome, has antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective action. The study in question was carried out using the chemotherapeutic agent 5-fluorouracil (5-FU), in which histopathological changes were observed in the intestinal mucosa of mice after its administration and, after treatment with rutin at a dose of 200 mg/ kg, a reduction in oxidative stress and reversal of the deleterious effects caused by this antineoplastic was observed.

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) published, in 2019, systematic reviews and guidelines on therapies for oral mucositis. One of the studies extends to post-chemotherapy intestinal mucositis and addresses the clinical improvement provided by glutamine supplementation, an L-alpha-amino acid, in patients undergoing chemotherapy, in addition to contributing to a better general nutritional status, reduction of sarcopenia and lymphopenia (ANDERSON P.M.; LALLA R.V, 2020).

Recent pilot studies also indicate that the use of Silymarin supplementation can significantly reduce the occurrence of diarrhea and nausea, through the inhibition of lipid peroxidation, antioxidant, antifibrotic, anti-inflammatory, immunomodulatory and membrane stabilizing effects achieved by the action of such drug (CHANG T.-K. et al., 2021). In addition, other studies

show that the use of Losartan in patients using antineoplastic medications was able to prevent histopathological changes, reduce inflammation and the release of free radicals (OLIVEIRA M.M.B. et al., 2021).

Furthermore, according to Chen G. et al. (2021), the G protein-coupled estrogen receptor (GPER) has a protective action on crypt cells, attenuating their apoptosis and proliferation, and on the DNA itself, which undergoes harmful modifications. Likewise, MSPC (Millettia Speciosa Polysaccharides) showed important results such as increased cytokine production, improved immunomodulatory activity and body weight, restoration of intestinal morphology, as well as the integrity of the mucosa, bringing numerous benefits and showing its high efficacy (CHEN X. et al., 2021). Finally, despite losartan preventing intestinal damage and increasing cytokine levels, as well as preventing histopathological and morphometric changes from chemotherapy, its effect was partial, requiring further studies focused on the benefits and harms of the drug (OLIVEIRA M.M.B. et al., 2021).

FINAL CONSIDERATIONS

Chemotherapy and radiotherapy treatments are highly effective in suppressing neoplastic cells, but due to their cytotoxic effect, they generate side effects, one of which is intestinal mucositis, considered one of the most common. Studies indicate that the drugs used cause associated cell damage and also generate a decrease in the diversity and quantity of beneficial intestinal bacteria. As a consequence, there is an increase in bacteria with greater pathogenic potential, and also a decrease in beneficial and gram-positive bacteria, resulting in intestinal dysbiosis that alters mucosal homeostasis. Chemotherapeutics based on 5-Fluorouracil, cause Chemotherapeutics based on 5-Fluorouracil, cause alterations that make the intestinal mucosa more susceptible to bacterial colonization. The drugs with the highest rates of manifestation and severity of mucositis are: methotrexate, cisplatin, irinotecan (CPT-11), oxaliplatin, irinotecan and 5-FU. Clinical pictures vary according to the type and dose of the drug used, the route of administration and duration of exposure and also the type of cancer, gender, ethnicity and age of patients, it is important to emphasize that underlying diseases such as diabetes or autoimmune disease lead to greater vulnerability to mucositis damage. The use of Silymarin supplementation can significantly reduce the resulting symptoms of mucositis. Studies also indicate the clinical improvement provided by glutamine supplementation, an L-alpha-amino acid, in patients undergoing chemotherapy, in addition to contributing to a better general nutritional status, reduction of sarcopenia and lymphopenia; Dimorphandra gardneriana also presents significant results with antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective action. In addition, Silymarin can also significantly reduce the occurrence of diarrhea and nausea. Faced with the increasingly significant increase in the incidence of cancer, it is essential to deepen studies such as those mentioned, in an attempt to reduce the intestinal involvement caused by chemotherapy treatments, in an attempt to not only improve the quality of life of patients undergoing treatment, but also to enable greater adherence to it, since intestinal mucositis is a considerable side effect in such a therapeutic approach.

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