Editorial   **Open Access**

Intestinal Mucositis Induced by Chemotherapy: an Overview

Raquel Silva Araújo[1] **and André Luis Branco de Barros**[2*]

[1]College of Pharmacy, Universidade Federal do Amapá, Rod. Juscelino Kubitschek, KM-02, 68.903-419, Macapá, AP - Brazil

[2]Faculty of Pharmacy, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, 31270-091, Belo Horizonte, MG - Brazil

[*]**Corresponding author:** Branco de Barros AL, Faculty of Pharmacy, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, 31270-091, Belo Horizonte, MG – Brazil; E-mail: brancodebarros@yahoo.com.br

Key Words:

Mucositis; Cancer; Chemotherapeutic; Immunomodulator

Introduction

A single layer of epithelial cells lined by mucosa composes the selectively permeable intestinal barrier. It possesses many functions, among them nutrients absorption. Besides, this barrier also separates mechanically the internal and external environment, being the center of interactions between the mucosal immune system and luminal contents, including microorganisms. Some proteins, such as the tight junction proteins, are specialized in controlling substances and fluids permeability through intestinal barrier. They settle a leaky barrier allowing the basal Trans cellular crossing of a few luminal antigens, the process known as bacterial translocation (BT) which is responsible activating the host's immune system. However, when this barrier undergoes damage, it results in increased intestinal permeability (IP) and, in sometimes, in BT across the intestinal mucosa, contributing to the development of inflammation and sepsis [1].

Among the different causes of intestinal barrier damages, mucositis induced by chemotherapy has gained enormous interest due to clinical implications in cancer patients [2,3]. Mucositis is a clinical term characterized by mucosal damage. It presents debilitating symptoms as intestinal and/or oral pain, vomiting, diarrhea, sore mouth and destruction of the gastrointestinal epithelium that contributes to poor absorption of nutrients and, consequently, weight loss [2]. This scenario might force a reduction in the chemotherapeutics dose leading to a worse prognosis [3,4]. In addition, mucositis has a considerable economic impact, due to high costs with patients' hospitalization in order to manage symptoms characteristic of this disorder. This disease had its study neglected until 2004 when the Guidelines for Mucositis was launched [5] being updated in 2014 [6]. In spite of some advances in the oral mucositis form, which is the more studied and reported in the literature, there is still a lack of information about the intestinal form of this disease.

Thus far, selectivity is the greatest drawback faced by chemotherapeutics. Typically, these drugs barely distinguish between tumor cells and high turnover cells (e.g. intestinal cells) leading to several side effects, such as mucositis. The development of mucositis can be divided into five phases; however, the presence of all phases is not mandatory for establishing the disease [7-9]. The first step, known as initialization phase, occurs after chemotherapy administration resulting in cell injury. This lesion might be a consequence of direct DNA damage and/or caused by generation of reactive oxygen species (ROS). Next, in the second phase, several events may occur simultaneously. The DNA damage caused by the chemotherapy and the presence of ROS promote activation of transcription factors, such as NF-kB, involved in regulation of cytokine expression and inflammatory adhesion molecules. These can lead to messenger activation that regulate intracellular gene transcription influencing the differentiation, proliferation of immune cells, as well as the activity of other cytokines. Some cytokines have a modulatory character such as IL-1, IL-2, IL-4, IL-6, IL-10, and TNF. As an example, there is a relationship between high cytokines levels (IL-6, TNF) and the development of intestinal mucositis induced by chemotherapy [10,11]. However, the activation and magnitude of each cytokine is related to the cytotoxic drug used [10]. In this phase, immunoglobulin A (IgA) is essential in maintaining intestinal homeostasis by commensal micro biota and preventing interaction between pathogenic microorganisms or toxins and mucosal surface [12]. Indeed, oral administration of IgA to patients undergoing chemotherapy has shown promising results in reducing gastrointestinal toxicity [13]. In addition, increased levels of IgA were observed after administrating immunomodulatory nutrients in an obstruction intestinal experimental model [14,15]. In the third phase, increased presence of pro-inflammatory cytokines induces accentuated tissue damage, leading to a vicious circle in which the signal amplification keep on increasing cytokines and oxidative stress levels, resulting in more intense tissue damage and apoptosis. The epithelium begins to lose integrity, which is exacerbated in the next phase, known as ulceration. This fourth phase is characterized by integrity loss of mucosal and tissue morphological changes [7-9]. Reduction of the villus' height in humans [16] and animals [11] were observed after chemotherapy treatment. Due to epithelium ulceration the intestinal barrier becomes weak, which could lead to BT increasing the risk of bacteremia and sepsis [7-9]. At this time, determining the intestinal permeability (IP) might be an important parameter to evaluate the extent of mucosal injury. An intact intestinal barrier is fundamental to prevent the passage of harmful substances from the lumen to the bloodstream. The IP can be measured using different substances, such as sugars or radiopharmaceuticals (e.g. 51Cr-EDTA and 99mTc-DTPA) [11,17]. Radioactive-based methods have been reported as preferable, since they are safe, easy, fast and reliable methods. Nevertheless, only few studies have been published using such technique to determine and monitor IP changes induced by chemotherapy [11]. Finally, there is the healing phase that usually occurs spontaneously one month after chemotherapy discontinuation. Although it is a phase poorly understood, it is known that there is a sub mucosal signaling that triggers stimulation, migration, differentiation, and proliferation of the intestinal epithelium [7].

Despite its clinical importance, there is no curative treatment for mucositis. Medications to relieve pain and diarrhea are used as a palliative method [18]. While no standard approach has proven efficacy, numerous agents are studied in an attempt to treat or alleviate

mucositis induced by chemotherapeutics [2,5,19]. Beneficial effects in animal experimental models after chemotherapy injury of immunomodulatory nutrients such as amino acids [20,21], fatty acids [11,22], antioxidants and vitamins [23,24], and probiotics [25] have been demonstrated. In addition, strategies to increase local drug delivery are also reported, such as the oral use of a mucoadhesive formulation containing antioxidants and anti-inflammatories [24]. Furthermore, the use of nanotechnology is well reported in the literature indicating reduction or even elimination of toxic effects of drugs in several organs [26]. Despite of this already envisioned benefit, only few articles have been reported studies about the impact of encapsulation on intestine toxicity [27].

In conclusion, many substances have demonstrated usefulness to manage intestinal mucositis induced by chemotherapeutics, but much more research is necessary until this approach can reach the clinical field. The intestine was neglected in the literature for many decades but gained attention recently by the increase of inflammatory bowel diseases cases worldwide. However, intestinal mucositis research is a very recent area and knowledge about pathobiology process of this disease still must improvements, especially a better understanding of the impact of chemotherapeutics on the host's micro biota. It was recently reported that patients undergoing chemotherapy presented an increased amount of intestinal pathogenic bacteria [28]. In addition, non-invasive standard diagnostic methods in order to detect malfunction and monitor intestinal consequences of chemotherapy is still a lack nowadays. Although much remains to be done to effectively bring these substances to clinics, we strongly believe that intestinal mucositis induced by chemotherapy is a promisor area to study once it will have a great impact in cancer care by increasing therapeutic efficacy, ameliorating patients life quality and also reducing hospitalizations.

References

1. Peterson LW, Artis D (2014) Nat Rev Immunol 14: 141-153.
2. Keefe DMK (2007) Curr Opin Oncol 19: 323-327.
3. Keefe DMK, Gibson RJ, Hauer-jensen, M (2004) Semin Oncol Nurs 20: 38-47.
4. Keefe DM, Sonis ST, Bowen JM (2008) Expert Opin Emerg Drugs (2008) 13: 511-522.
5. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, (2004) Cancer 100: 2026-2046.
6. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, et al. (2014) Cancer 120: 1453-1461.
7. Sonis ST, Elting LS, Keefe DM, Peterson DE, Schubert MM, et al (2004) Cancer 100: 1995-2025.
8. Sonis, ST (2004) Nat. Cancer Reviews 4: 277-284.
9. Sonis, ST (2004) J.Support.Oncology 2:21-32.
10. Logan RM, Stringer AM, Bowen JM, Yeoh AS, Gibson RJ, et al. (2007) Cancer Treat Rev 33: 448-460
11. Beutheu S, Ouelaa W, Guérin C, Belmonte L, Aziz M, et al (2014) Clin Nutr 33:694-701.
12. Ferreira TM, Leonel AJ, Melo MA, Santos RRG, Cara DC et al. (2012) Lipids 47: 669-678.
13. Corthésy, B (2013) Autoimmunity Reviews 12: 661-665.
14. Peterson LW, Artis D (1999) Bone Marrow Transplant 24:35-9
15. Generoso SV, Viana ML, Santos RGC, Nogueira-Machado JA, Correia MITD, et al. (2010) Arch Microbiol 192: 477-484.
16. Viana ML, Dos Santos RD, Generoso S dV, Nicoli JR, Martins F Dos S, et al. (2013) Amino Acids. 45: 1089-1096.
17. Keefe, DMK, Brealey J, Goland GJ, Cummins AG (2000) Gut 47:632-637.
18. Demeo MT, Mutlu EA, Keshavarzian A, Tobin MC. J.(2002) Clin. Gastroenterol 34: 385-396.
19. Sebille YZAV, Stansborough R, Wardill HR, Bateman E, Gibson RJ, et al. (2015) Curr Oncol Rep (2015) 17:50
20. Posner MR, Haddad RI (2007) J Support Oncol 5:33-39.
21. Nose S, Wasa M, Tazuke Y, Owari M, Fukuzawa M (2010) J Parenter Enteral Nutr 34: 530-537.
22. Koppelmann T, Pollak Y, Mogilner J, Bejar J, Coran AG ,et al.(2013) Br J Nutr 109:89-98.
23. Bodiga VL, Bodiga S, Surampudi S, Boindala S, Putcha U, et al. (2012) Nutrition 28: 572-580.
24. Filho EXS, Ávila PHM, Bastos CCC, Batista AC, Naves LN, et al. (2015) Toxicology Reports.
25. Whitford EJ, Cummins AG, Butler RN, Prisciandaro LD, Fauser JK, et al. (2009) Cancer Biol Ther 8:505-511.
26. Leite, EA, Souza CM, Carvalho-Junior AD, Coelho LGV, Lana AMQ et al. (2012) I J Nanomedicine 7: 5259-5269.
27. Lu WL, Qi XR, Zhang Q, Li RY, Wang GL, et al. (2004) J Pharmacol Sci 95: 381-389.
28. Vanhoecke B, Stringer A (2015) Curr Opin Support Palliat Care 9: 174-181