ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 07, Issue, 09, pp.15347-15352, September, 2017

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

MAIN PREDICTORS IMMUNOMODULATORIES OF CANCER

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ARTICLE INFO

Article History:
Received 22nd June, 2017
Received in revised form
08th July, 2017
Accepted 19th August, 2017
Published online 30th September, 2017

Key words:

Immunotherapy,
Nutrition Therapy,
Neoplasm,
Immunologic Factors,
Glutamine,
Arginine.

ABSTRACT

Background: In the world, the highest incidences in the scenario of cancerous diseases in 2016 were those of lung cancer with 1.9 million, breast 1.8 million and colorectal 1.5 million. In Brazil, 580,000 new cases of cancer were estimated by 2014. In addition, protein-energy malnutrition, which occurs in 30,0-90,0 % of cancer patients, also causes adverse effects on the immune system.
Objective: The goal of this paper was to describe in a brief and objective way, the important role of imunomodulators for the treatment of oncologic patients.
Methodology: A literature review was carried out aiming at searching the most relevant data base: PubMed/Medline, LILACS, SeCS (Serials in Health Science), with keywords indexed by Bireme: (*imunomodulators, cancer, nutritional therapy).*
Conclusion: This work allowed to evaluate the benefits of immunomodulating supplementation in patients with cancer by reducing the effects of septic and inflammatory complications. Imunomodulators have features that are capable of besides improving radiotherapy and chemotherapy treatment efficacy, are also able to delay tumor growth.

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Citation: Ana Valeria Garcia Ramirez, Idiberto José Zotarelli Filho, Maria Christiane Valéria Braga Braile-Sternieri *et al.* 2017. "Main predictors immunomodulatories of cancer", *International Journal of Development Research*, 7, (09), 15347-15352.

INTRODUCTION

In the world, the highest incidences in the scenario of cancerous diseases in 2016 were those of lung cancer with 1.9 million, breast 1.8 million and colorectal 1.5 million 1. The latter was the third most common type of neoplasm among men. In Brazil, 580,000 new cases of cancer were estimated by 2014. Colon and rectum cancer appears as the third most incident, with estimates of 33,500 new cases and 15,000 deaths from the disease (Flower *et al*., 2017). Moreover, more than 90.0 % of this neoplasm affects individuals over 50 years of age, presenting a relatively slow development and a five-year survival rate of up to 80.0 % in the initial stages and 5.0 % in the stages more advanced. Surgery is the most frequent treatment of colorectal cancer (Barbosa *et al*., 2015). In this context, immune function is usually suppressed by surgical procedures, leading to increased morbidity, mortality, and length of hospital stay. In addition, protein-energy malnutrition, which occurs in 30-90 % of cancer patients, also causes adverse effects on the immune system (Davarpanah *et*

al., 2017; Flower *et al*., 2017). Immunonutrition becomes an option of therapeutic approach for these patients, reducing the incidence of postoperative complications, since it modulates the immune system and the inflammatory response of the organism. Immunomodulatory diets include glutamine, arginine, omega-3 fatty acids and nucleotides (immunonutrients), isolated or combined, and improve defense mechanisms after large surgeries and are generally used in the preoperative period (Flower *et al*., 2017; Barbosa *et al*., 2015).

According to the guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN), the use of immunomodulatory formulas in elective upper gastrointestinal tract surgeries has evidence level A. According to the National Consortium of Oncology Nutrition, there are proven benefits in using Of immunomodulating diets in patients preoperatively of elective oncologic surgeries (Davarpanah *et al*., 2017; International Agency for Research on Cancer. GLOBOCAN 2012). Cancer is the term used for a group of diseases that can affect any part of the body (Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2014; Fortes *et al*., 2007; Fey *et al*., 2010; Castro, 2005). Malignant tumors and neoplasms are also used as nomenclature. Cancer is considered the disease with the greatest cause of death in the world (Krause, 2005). A chronic multicausal disease, characterized by the division and reproduction of abnormal cells. According to Krause *et al*. (2005) "When damaged cells escape the proper mechanisms to protect the body from the growth and spread of such cells, neoplasia is established." This rapid production of abnormal cells may subsequently invade adjacent regions of the body and spread to other organs, metastasis (Krause, 2005; Who. World Health Organization. Cancer. Fact Sheet n297. Fev 2012). According to the World Health Organization (WHO), the rate of premature death from cancer is fourteen million people each year, being the second most common cause of death in most countries. For the 160 countries with 2010-2015 data, the percentage of cancer countries increased from 81.0 % in 2010 to 86.0 % in countries with new diseases in 2015 (Who. A global snapshot in 2015 summary of results from the 2015 who ncd country capacity survey, 2014). Cancer is expected to account for 80.0 % of the estimated 20 million new cases by 2025 (Estimativa 2016: incidência de câncer no Brasil / Instituto Nacional de Câncer José Alencar Gomes da Silva – Rio de Janeiro, 2015). In Brazil, there are about 600 thousand new cases of cancer, being the second cause of death due to disease, only surpassed by cardiovascular diseases (Pinho *et al*., 2004). The disease has several causative factors, among which the inadequate diet stands out as one of the main causes, accounting for 35% of the neoplasms diagnosed, followed by smoking (30%) and others, such as conditions and type of work, alcoholism, pollution and Food additives (Guerra *et al*., 2005ç). Treatment of the disease involves chemotherapeutic drugs that reduce food intake by promoting nutritional losses (Vannucchi and Marchni, 2007), causing a depletion of nutritional status, with decreased immune function - the body's primary defense against invading pathogens, unsafe components and cancer cells. Thus, immunomodulation is important, a therapeutic approach to intervene in the self-regulation processes of the defense system (Bozzetti, 1992).

According to Silva *et al*., There are changes in the energetic metabolism of the individual with cancer, because the cancer cell primarily uses glucose as an energy substrate, thus increasing up to 50 times the consumption, compared to normal cells. Muscle amino acids are used to maintain plasma glucose levels (Silva, 2006). It is estimated that an adequate diet would be able to prevent three to four million new cases of cancer each year (Garófolo, 2004). Malnutrition of cancer patients is one of the main factors associated with postoperative complications. Several studies have indicated nutritional therapy in the adult oncology patient, with the aim of preventing or reversing the worsening nutritional status, avoiding a cachexia, thus improving the patient's quality of life (Inca - Instituto Nacional do Câncer. Consenso nacional de nutrição oncológica. Instituto Nacional de Câncer, 2009). Dietary supplementation with nutrients that improve immune function becomes indispensable since some specific nutrients have immunological effects, called immunonutrients, they are: arginine, omega-3 fatty acids, glutamine, nucleotides, beta-carotene and / or branched-chain amino acids (Novaes and Pantaleão, 2005). Based on these data, the objective of this study was to describe the importance of immunomodulators in the treatment of cancer patients.

MATERIALS AND METHODS

The bibliographic study was developed using the procedure of consultation and investigation of the scientific literature in the databases PubMed / Medline, LILACS, SeCS (Health Sciences). Key words indexed by Bireme were: immunomodulators, cancer, nutritional therapy, employed in the search for scientific articles and multiple theoretical reference. When performing the selective reading, only those that were in agreement with the subject of the research were selected.

Mesh Terms

The words were included “immunomodulators”,”cancer”, “nutricional therapy”. For further specification, the "Cancer" description for refinement was added during searches. It was stipulated deadline, and the related search covering all available literature on virtual libraries.

Series of Articles and Eligibility

A total of 200 articles were found involving *immunodulators in cancer*. Initially, it was held the exclusion existing title and duplications in accordance with the interest described this work. After this process, the summaries were evaluated and a new exclusion was held. A total of 120 articles were evaluated in full, and 58 were included and discussed in this study.

Development

According to Hallay *et al*. (2002), immunonutrition is a form of artificial feeding that renews cells for immune response. Involving specific amino acids called immunomodulators such as glutamine, arginine and fibers. As the main factor associated with cancer complications is linked to nutrition, a differentiated diet is necessary to improve the defense mechanisms of cancer patients. The change in nutritional status, very common in cancer patients, is manifested in all types of cancer, varying its intensity with the type and location of the tumor (Alves *et al*., 2009). The greater the surgery and the type of trauma, the more severe are the alterations of the defense mechanisms, making these patients susceptible to sepsis and inflammatory complications. Diets should be enteral supplemented with glutamine, arginine and omega-3

fatty acid, and have shown in several studies improved response in the period following large operations, reducing the risk of sepsis and trauma (Wu *et al*., 2001; Garófolo and Petrilli, 2006).

Main immunomodulators

Immunomodulators are nutrients capable of modulating the immune system, thus enhancing the defense mechanism. These nutrients are: arginine, omega-3 fatty acids, glutamine, nucleotides, micronutrients and antioxidant vitamins. They act by modulating the immune-inflammatory response, thus maintaining the integrity of the intestinal mucosa, improving both the clinical status and the nutritional status of cancer patients (Barbul *et al*., 1990; Campos *et al*., 2002).

Arginine

L-arginine is a non-essential amino acid, with an important role in protein synthesis, acting in the improvement of vasodilatation, very interesting in the treatment of patients with cardiovascular diseases (Vissers *et al*., 2003; Lind, 2004). Arginine is a stimulant of pituitary growth hormone (GH) and is related to the increased activity of NK cells, Helper T cells and stimulating the production of cytokines such as IL-1, IL-2, IL-6, TNF- A (Novaes *et al*., 2003). In addition, several studies and clinical trials have shown that its dietary supplementation is able to improve T14 cell response and reduce tumor growth rates (Daly *et al*., 1992), in addition to increasing the survival time of cancer patients (Buijs *et al*., 2010). Promoting also the increase of immunity through the release of growth hormone, stimulus in the production of nitric oxide, hydroxyproline, cytokines and polyamines (Novaes and Beal, 2003). According to Novaes *et al*. (Wu *et al*., 2000), oral supplementation of 50mg / kg / day of arginine over a period of one year in rats reduced the total number of tumors and increased their survival. Studies have shown that during the early stage of carcinogenesis, supplementation with L-arginine (1.0 % in drinking water) has resulted in decreased production of rectal tumor and hyperproliferation of dead cells (Kim, 2011).

Glutamine

Glutamine is the most abundant amino acid in the body and during severe metabolic stress it undergoes a fall in the body. It is synthesized in the skeletal system and secreted in the bloodstream, thus reaching the tissues. The main glutamine consuming cells are the renal, hepatic, and intestinal cells and the immune system (Cetinbas *et al*., 2010). Glutamine protects the body against septic shock by preventing glutathione depletion and thereby reducing cell death, which occurs during shock. In surgical and oncology patients, glutamine supplementation decreases the production of some proinflammatory cytokines (Boligon and Huth, 2011). The use of glutamine can lead to reduced hospitalization time due to its effect of delaying the inflammatory response of cytoreduction, activating the T lymphocytes of cancer patients. In addition, it may decrease the toxic effects of radiotherapy and chemotherapy by improving the quality of life of the neoplastic patient (A.S.P.E.N, Board of Directors. Clinical Guidelines. Position Paper: Parenteral Nutrition Glutamine Suplementation, 2011). According to ASPEN - American Society for Parenteral and Enteral Nutrition, it is indicated as an ideal dose of glutamine supplementation 0.5g / kg / day. Doses greater than 0.2g / kg / day are able to decrease complications by infection in surgical patients when compared to lower doses (Frenhani, 2006). With its immunomodulatory role, glutamine stimulates lymphocyte multiplication, B-cell differentiation, interleukin-1 production, and macrophages phagocytosis. Adequate stock of glutamine proliferates NK cells, a type of lymphocyte important in fighting tumor cells and viral infections. Another function of glutamine is the local immune stimulating effect, stimulating the body's overall immune function (Carmo and Correia, 2009).

Omega 3 Fatty Acids

Fatty acids, previously seen as a way of storing energy, today with some evidence, can be determinant of syndromes that can lead to death, if the diet is poor in these nutrients (Faintuch, 2006). Fatty acids, also called AGs n-3, have anti-thrombogenic, immunomodulatory and anti-inflammatory properties (Zain, 2001), which may modify the carcinogenesis process, such as suppression of eicosanoid biosynthesis, resulting in altered immunological response of tumor cells And modulation of inflammation (Frenhani, 2006). Long-chain polyunsaturated fatty acids (Eicosapentaenoic - EPA and docosahexaenoic - DHA), present in fatty fish, have a great impact on the inhibition of carcinogenesis, increasing the efficacy of radiotherapy and several chemotherapeutic drugs, as well as slowing growth Of tumors (Frenhani, 2006).

Nucleotides

Nucleotides are the structural units of DNA and RNA with the function of improving healing and the immune system (Davarpanah *et al*., 2017). They also participate in the formation of ATP, thus influencing metabolic processes. Hardly found in food sources, requiring food supplementation (Davarpanah *et al*., 2017).

Antioxidant vitamins

The modulation of the immune system is performed by a set of antioxidant nutrients being therefore the vitamins A, E and C important contributing factors in decreasing cancer. In addition to the antioxidant activity, they are also responsible for the modulation of carcinogenic metabolism, alteration of cellular transformation and differentiation, inhibition of cell proliferation, oncogenic expression and endogenous formation of carcinogens (Geervani and Arundhathi, 1981). Vitamin A, known as retinoic acid, and provitamin A, known as beta-carotene, have important characteristics for maintaining the structure and integrity of epithelial cells, and are necessary for the immune response of B and T lymphocytes, considered to be capable of exerting a Protective effect against cancer (Lotan, 1996). Retinoids have a preventive chemo activity in some types of cancers, this is due to the action of retinoic acid on the expression of genes involved with cell differentiation and proliferation (Potischman *et al*., 1991). Vitamin C, also known as ascorbic acid is a water soluble and antioxidant vitamin that reacts directly with the simple oxygen, hydroxyl radical and superoxide radical, in addition to regenerating vitamin E, has the function of avoiding the formation of carcinogens from precursor compounds, Inhibiting carcinogenesis by the following mechanisms: alteration of carcinogenic structure, competitive inhibition, prevention of carcinogenic access to target tissue by increasing membrane stability (Anthony and Schorah, 1992; Ames *et al*., 1995).

Vitamin E is a non-enzymatic, liposoluble and structural antioxidant of the cell membrane, a component of membranes, mucosa and epithelial tissue important for maintaining tissue integrity, combating free radicals, thereby able to inhibit cancer formation by acting In DNA stability, avoiding breakage and damage to chromosomes and enhancing DNA repair (Claycombe and Meydani, 2001; Konopacka *et al*., 1998; Bargellini *et al*., 2003). Its deficit is associated with decreased immune response and hypersensitivity.

Zinc

Antioxidant nutrients are important in structural function and as cofactors of several enzymes in the etiology of cancer. Zinc is a cofactor of several enzymes that act on cell replication, immunity, oxygen free radicals and maintenance of the integrity of deoxyribonucleic acid (Kapil *et al*., 2004). Its association with cancer has been the target of several authors, in which they analyzed in their work the concentration of plasma zinc, showing hypozincemia in cancer patients (Mafra, 2005). Zinc deficiency in the body contributes to oxidative changes in DNA, which increases the risk of cancer, and zinc is therefore an important nutrient, since it acts on the antioxidant defense and DNA repair (Lipman *et al*., 1987). In a study by Lipman *et al*. (Anthony and Schorah, 1992), compared plasma zinc concentrations in patients with esophagitis, esophageal cancer, and healthy subjects, and the results showed that plasma zinc concentration in cancer patients (56 3 g dL^{-1}) was significantly lower than that of Patients with esophagitis (72 5 g dL^{-1}) and the group of healthy subjects (78 5 g dL^{-1}). Immunomodulators and their function in the different types of cancer. Several studies have shown that supplementation of immunomodulatory nutrients in patients with neoplasias in various parts of the body has obtained favorable effects for the treatment and recovery of these patients, helping to stabilize the catabolism and reduce the peroxidative damage that are due to the disease (Garófolo, 2004; Garófolo and Petrilli, 2006).

Breast cancer

According to Cho-Chung *et al*. (Van Bokhorst-de Van der Schueren *et al*., 2001) in an in vitro study confirmed previous findings that cyclic dibutyl AMP and L-arginine inhibit the growth of breast tumors, suggesting that these components have a therapeutic potential for the treatment of Breast cancer in humans.

Head and neck cancer

Researchers in 2001 studied the effect of enteral nutrition supplemented with L-arginine on nutritional status, immune response, postoperative complications, and survival of 49 patients with head and neck cancer undergoing surgery. The studies found that patients who received L-arginine supplementation had an increase in survival time (Read *et al*., 2007). According to Boligon *et al*. (2011) in their study with 16 patients with head and neck cancer, received 20.0 g of glutamine diluted in 40.0 mL of water, verifying that the supplemented patients had better prognoses. Supplementation provided lower prevalence and severity of mucositis during radiotherapy and / or chemotherapy compared to the control group (without glutamine ingestion). And the Nutrition Risk Index increased in patients without glutamine. ASPEN (Frenhani, 2006) suggests that burn patients and patients with head and neck cancer should be supplemented with arginine and other immunomodulators, with lower incidences of complications. It is recommended to consume 5.0 g per day. Doses above 4.0% of the total caloric load lead to loss of beneficial effects both immunological and nitrogen retention, increasing mortality in sepsis.

Colorectal cancer

A study by Read *et al*. (Santos and Novaes, 2011) assessed the impact of n-3 GAs on colorectal cancer patients undergoing chemotherapy. Patients received 480 mL / day oral eicosapentaenoic acid (EPA) supplement for 3 weeks, pre-chemotherapy, and extended for another 9 weeks (corresponding to 3 cycles of chemotherapy). At the end of the study, 15 patients were evaluated, and it was observed that the use of EPA supplemented orally reduced weight loss and increased lean mass, improving the nutritional status, quality of life and functional capacity of cancer patients. According to some studies, glutamine acts in the protection of the gastrointestinal mucosa, stimulates the growth of the intestinal mucosa, reducing the changes in intestinal absorption and permeability, being therefore a nutrient with protective effects of patients with metastatic colorectal carcinoma who are under chemotherapeutic treatment (Sharma *et al*., 2005).

Ovarian cancer

Sharma *et al*. (2005) investigated the effect of n-3 AGs on the growth of four cell lines of ovarian epithelial carcinoma. These lines were treated with n-3 GAs and evaluated for cell proliferation, apoptosis and expression of vascular endothelial growth factor (VEGF). A significant inhibitory effect was observed in all four lines, suggesting that under the effect of n-3 AGs there are definitely suppressive growth mechanisms.

Conclusion

The study demonstrated that an adequate diet with immunomodulatory nutrients brings several benefits for the treatment, prevention and improvement of cancer patients with various neoplasms. Its relation with the general immunological state of the organism has an extreme influence on the survival and improvement of the quality of life of cancer patients. Immunomodulators have characteristics that are capable of besides increasing the effectiveness of the radiotherapeutic and chemotherapeutic treatments, also being able to delay the growth of the tumors.

Conflict of interests

There is no conflict of interest between authors.

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