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NEUTROPENIC FEVER IN ONCOLOGICAL PATIENTS: CHARACTERISTICS OF THE TREATMENT AND THE MAIN BIOCHEMICAL MARKERS

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Abstract: Febrile neutropenia is a clinical complication in patients diagnosed with cancer and undergoing chemotherapy, which in turn leads to a condition of immunosuppression, making the patient vulnerable to infections to various microorganisms, and as a consequence the patient undergoing cancer treatment develops a more severe neutropenic condition. It is necessary to discuss the occurrence of febrile neutropenia in cancer patients, a measure adopted to prevent infectious conditions, with an inversely proportional relationship between infections by microorganisms and the decrease in the number of blood neutrophils in cancer patients, given the infectious context in which the cancer patient is exposed due to chemotherapy treatment, antibiotic therapy applied to patients with febrile neutropenia will be essential for professionals involved in the treatment of the patient for a positive recovery in the face of febrile neutropenia, thus avoiding a negative prognosis in the treatment of the cancer patient. The altered biochemical markers in cases of febrile neutropenia is also a parameter used for the follow-up of the oncological patient, clearly aiming at an approach regarding both the treatment of the oncological patient when he develops febrile neutropenia.
Keywords: Febrile Neutropenia, Cancer, Antibiotic therapy, Neutrophils.

INTRODUCTION

"Cancer is caused by a series of somatic changes in DNA that lead to unrestricted cell proliferation." (MORIN, 2017) According to Clark and Longo (2017, p. 1) "cancers are characterized by uncontrolled cell division, evasion of cell death, tissue invasion and the ability to metastasize".

Its treatment involves several individual or combined therapeutic approaches, which can be applied locally or systemically,

such as surgery, radiotherapy (including photodynamic therapy) and ablative approaches as forms of local treatment, as well as chemotherapy (hormone and molecular target therapy) (including immunotherapy) as systemic treatments. (SAUSVILLE and LONGO, 2017; FERREIRA et al., 2017)

Most of these treatments are cytotoxic, or have toxic effects on the organism, especially chemotherapeutic agents, mainly because they act both on the carcinogenic target tissue and on normal tissues peri or distant from it. One of these potential and most common toxic effects is myelosuppression, which secondarily generates greater susceptibility of these patients to infections. (SAUSVILLE and LONGO, 2017; FERREIRA et al., 2017)

Neutropenia, a decrease in plasma neutrophil counts, may or may not be accompanied by fever. The presentation of infectious syndromes (in tissues, organs, or systems) in the oncologic patient with neutropenia can greatly differ from the non-neutropenic patient. Due to the decrease in neutrophil counts, the former may not show classic and early signs and symptoms of infection, however, the most common and sometimes the only clinical sign presented in neutropenia is fever. It must be noted that patients with severe neutropenia may not have fever or even be hypothermic in the presence of infectious processes. (SAUSVILLE and LONGO, 2017; FERREIRA et al., 2017; RIVERA-SALGADO et al., 2018)

In cancer patients, the presence of fever associated with neutropenia, the so-called febrile neutropenia (NF), is an oncological emergency because there are high risks of complications, increased hospitalization and mortality rates. According to ASCO (American Society of Clinical Oncology), the rate of complications such as hypotension, renal failure, respiratory and heart failure due to NF, is between 25 and 30%, and mortality exceeds 11%. (FERREIRA et al., 2017 and RIVERA-SALGADO et al., 2018)

"In the setting of severe sepsis or septic shock, in-hospital mortality can be as high as 50%". (TAPLITZ, 2018)

Currently, there are several biomarkers used to identify the beginning and course of an infection, among them some already well established in clinical practice for their predictive value or in the early identification of a diagnosis, as is the case of C-reactive protein (CRP) and procalcitonin (PCT). As well as these, other biomarkers can help not only the identification but also the adequate and early therapeutic management of febrile neutropenia.

Since infections are a common cause of morbidity and mortality in cancer patients, especially those with neutropenia resulting from treatment, prevention and the institution of rapid therapeutic drugs are necessary to modify and interrupt unfavorable clinical outcomes in these patients. Among others, but primarily due to the prophylactic use and early initiation of empirical antibiotic therapy, this has been possible in these patients, and the mortality rate due to NF has been lower than 10% since 2013. (FINBERG, 2017)

Thus, due to its clinical and prognostic importance, a better understanding of NF in cancer patients, its early identification through biomarkers and the institution of an adequate treatment become the subsequent themes developed in this chapter.

NEUTROPENIA - CONSEQUENCE OF CHEMOTHERAPY TREATMENT

Cancer patients carry with them problems that develop during the stage of the disease and its treatment. Among the various acquired problems is febrile neutropenia, a common consequence when the diagnosis is made and chemotherapy is started. Cancer cells are extremely powerful, they multiply in

a disorderly and uncontrolled way, invading the entire body and making it sick. Some procedures are used to combat these cells, including the use of chemotherapeutic agents that, in addition to destroying cancer cells, end up destroying healthy ones, especially those of the immune system (MIYAHARA, 2013). Blood cells are produced in the bone marrow, they are: white blood cells, red blood cells and platelets. They are in constant renewal and the use of chemotherapy leaves them sensitive, especially those of immunity that are responsible for the defense of the organism against pathogens. Cancer and its treatment alter immunity, decreasing the number of neutrophils in the blood. The main causes of febrile neutropenia are in the individual who is already weakened by cancer and its treatment, associated with frequent infections resulting from gram-negative bacteria, normally provided by the gastrointestinal flora; gram-positive bacteria, normally provided with the respiratory system; viral and fungal infections among other types (MIYAHARA, 2013). Neutrophils are the target cells of neutropenia. Such cells attack and destroy bacteria. One of its main functions is phagocytosis, which means cellular ingestion of the offending agent:

> Neutrophils that penetrate tissues are already mature cells, capable of immediately initiating phagocytosis. When approaching the particle to be phagocytosed, the neutrophil first latches onto the particle and then emits pseudopods in all directions around the particle. This creates a closed chamber containing the phagocytosed particles.

The chamber then invaginates into the cytoplasmic cavity and breaks its connections with the cell's outer membrane to form a phagocytic vesicle (also called a phagosome) that floats freely in the cytoplasm. A single neutrophil can, in general, phagocytose about three to 20 bacteria, before being inactive and dying (GUYTTON, 2011). To diagnose a patient with febrile neutropenia, a count of the number of neutrophils in the bloodstream is necessary. The patient will be considered neutropenic when this count is below 500 cells 12 per cubic millimeter. Values lower than 100 cells per cubic millimeter make the patient more vulnerable to the development of infections, as their emergence is inversely proportional to the number of neutrophils (NEUENSCHWANDER, 2009).

According to Velascos, 1998: "The rapid decline of neutrophils towards neutropenia and its long duration are described as the main risk factors causing febrile complications in cancer patients". The impairment of the number of neutrophils, due to the patient's exposure to infectious agents, can complicate the individual's clinical condition, leading to severe, systemic infections and even death. However, there is an increase in the number of hospitalizations and the demand for technology for diagnosis, thus overloading the unified health system economically and physically. Post-chemotherapy in cancer patients compromises the number of neutrophils in the bloodstream, as antineoplastic chemotherapy can affect the bone marrow, which is responsible for producing blood components. Consequently the individual will be immunologically affected. People with any type of cancer that affects bone marrow tissue, such as leukemia and myeloma; or patients undergoing radiotherapy, all these factors will contribute to the individual developing a more severe neutropenia (SILVA, 2018). According to SILVA 2018., "Febrile neutropenia is present in more than 80% of patients who have onco-hematological diseases. Most episodes of neutropenia occur within the first 14 days after chemotherapy. Patients with febrile neutropenia are at risk of developing infection with any type of microorganism including bacteria, fungi and

viruses." When penetrating the bone marrow and other organs, the leukemic cells impair or prevent the process of normal hematopoiesis. Patients begin to present with anemia, bleeding, and fever without an infectious focus due to neutropenia. In addition to the decrease in the number of neutrophils, other factors may influence the onset of this adverse event, febrile neutropenia, such as advanced age (>65 years), reduced body surface area, previous bone marrow involvement, among others. As a consequence of the appearance of neutropenia, the health team must develop strategies to control this event and the interference in the dosage of chemotherapy is highlighted. This method can negatively interfere with the patient's therapeutic outcome (NASCIMENTO, ANDRADE, et al., 2014).

CLASS OF ANTIBIOTICS INTENDED FOR THE TREATMENT OF FEBRILE NEUTROPENIA

In the past, when a patient had febrile neutropenia as a result of the use of chemotherapy drugs, for drug treatment to begin, it was necessary to wait for the isolation of the microorganism causing the infection or to define more precisely the focus of the infection so that adequate treatment could be initiated. But scholars at that time, when noticing high mortality rates due to infections that were not immediately treated, found that the focus was not clearly identified and that when analyzing the cultures of microorganisms, most of them were negative. And that was how the empirical use of broad-spectrum antibiotics intravenously began in the hospital setting. With this strategy, they managed to reduce mortality cases (BELLESSO, COSTA, et al., 2010). Due to not knowing for sure the type of bacteria to which the individual is subjected, when admitted to a hospital network, treatment with broad-spectrum antibiotics must be started as soon as possible, as the infection can progress and worsen the clinical condition of the patient, which can lead to the death of neutropenic. The class of antibiotics used in emergency are the beta-lactams, this class has a bacterial activity against pseudomonas, they are: cefepime, piperacillin+tazobactam, meropenem, among others (ROSAS et al., 2019). Beta-lactams are responsible for hindering the production of peptidoglycan, a substance that makes up the bacterial cell wall. Carbapenems are the most famous of this class, as they have a broader spectrum of activity than most beta-lactams. The best known among them is imipenem associated with cilastatin, which binds to the proteins that bind penicillins, thus interrupting the cycle of restructuring the bacterial cell wall (BRUNTON, 2012).

Beta-lactams have in common, in their chemical structure, the beta-lactam ring, which is responsible for the death of bacteria due to its bactericidal characteristic. This group includes penicillins, cephalosporins, carbapenems and monobactans (ANVISA, 2007).

The subclasses of beta lactams are separated according to the radical that is attached to the beta lactam ring composed of three carbon atoms and one nitrogen. The thiazolidine, dihydrothiazine, pyrrolic rings, linked to the beta lactam ring, characterize the groups of penicillins, cephalosporins and carbapenems. Monobactams do not have a ring as a radical. Therefore, each group of antibiotics that have the beta lactam ring will have, in their chemical processes, distinct pharmacological characteristics, such as receptor affinity and spectrum of action (ARRUDA, SIQUEIRA, et al., 2019). Penicillins were discovered thanks to Alexander Fleming in 1928. The first penicillins used were benzylpenicillins (penicillin G) and their similar. It is the most chosen drug to treat infections such

as bacterial meningitis, skin and soft tissue infections, syphilis, among other diseases. But they are quite sensitive to beta-lactamases and their difficulty in absorption through the gastrointestinal tract requires them to be administered intravenously (RANG, et al., 2017).

Because they are vulnerable to the action of beta-lactamase, most of these drugs contain substances that inhibit the beta-lactamase enzyme. Examples include clavulanic acid, sulbactam and tazobactam. Such substances, when well associated, can expand the drug's spectrum of action (AZEVEDO, 2014). They are widely distributed throughout the body, lipoinsoluble and do not penetrate mammalian cells. When meningitis is inflamed, these compounds are able to overcome the blood-brain barriers, achieving excellent therapeutic concentrations in the cerebrospinal fluid. Excretion is carried out through the kidneys and they have a short plasma half-life (RANG, et al., 2017). The first cephalosporin was discovered in 1945 by Giuseppe Brotzu. This subclass is divided into five groups, which are characterized according to the spectrum of action and chemical substances added to the cephalosporin molecule. The first generation cephalosporins were the first to be produced, they are effective against some species of Staphylococcus and Streptococcus. They are more active against gram-positive bacteria than second-generation bacteria (AZEVEDO, 2014). The second-generation ones appeared around the 70's, being more used for groups of gram-negative bacteria that produce beta-lactamase. The third generation appeared in the late 70's, these are broad spectrum and are more used for nosocomial infections. The fourth-generation ones are more potent against gram-positives than the third-generation ones and have more resistance to degradation by the beta-lactamase enzyme. Finally, we have the fifth generation, the latter has a high potential against multidrug-resistant bacteria (AZEVEDO, 2014). Cephalosporins are broad-spectrum beta lactam antimicrobials. They are water-soluble agents and can survive in acidic environments. Treatment with cephalosporin is often started empirically. This class of drugs is intended for many infections such as septicemia, pneumonia, biliary tract infections, sinusitis, among others. They can be administered orally due to their good acceptance in acidic environments. Its excretion is done by the kidneys and bile (RANG, et al., 2017).

Carbapenems are the last to be chosen for the treatment of some infections. They are extremely effective against resistant bacteria and are the group with the widest spectrum. Such substances have a powerful enemy, carbapenemases, enzymes produced by resistant bacteria that hydrolyze most beta-lactams (ARRUDA, SIQUEIRA, et al., 2019). Among the most used carbapenems are imipenem associated with cilastatin; such compound has the function of blocking the enzyme DHI, meropenem and ertapenem. They are broad-spectrum antibiotics and are stable in the presence of beta lactamases. Their administration must be intravenous or intramuscular, they do not have a good oral absorption and their excretion is predominantly renal (RANG, et al., 2017). Unlike other antibiotics, monobactans lack good bacterial activity. They do not act on gram-positive bacteria, being restricted only to gram-negative and facultative bacteria (AZEVEDO, 2014). Beta lactam antibiotics have low toxicity because they act on the cell wall, such tissue is not present in human eukaryotic cells, and has a high therapeutic efficacy. Like all other antibiotics, they must be used with caution because their use for a long time and high doses can harm human cells and cause the famous super resistant bacteria (ARRUDA and SIQUEIRA, et al., 2019).

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ALTERATION OF BIOMARKERS IN FEBRILE NEUTROPENIA

The fact that the neutropenic patient has high temperatures and a low number of neutrophils does not denounce a life-threatening infection to the health professional. Infections accompanied by febrile neutropenia due to chemotherapy are a very serious oncological emergency that requires other types of indicators to better diagnose the disease (KIRAL, et al., 2016). Endocan, for example, has already been studied in patients with febrile neutropenia. As it is a specific molecule of endothelial cells, it is closely related to cancer and sepsis, interfering with the severity of these two problems. Therefore, monitoring serum levels of endocan is extremely effective for the treatment of febrile neutropenia (KIRAL, et al., 2016). In terms of research, according to the article:

> In neutropenic patients, symptoms and clinical findings are seen more often than expected in inflammation and infection, and in most cases, the only symptom is fever. In this study, increased serum levels of endocan were observed in children with febrile neutropenia. A previous study showed that serum levels of endocan increased during complicated bacterial infections before a decrease was observed during antibiotic therapy in adult patients with leukemia (KIRAL, et al., 2016 p.8).

Endocan binds to bioactive molecules that are associated with cell signaling and adhesion, such as tumor necrosis factor (TNF) and interleukins. Together with these cells it manages to regulate cell proliferation, differentiation, migration and adhesion. Serum levels of endocam are associated with inflammation and tumor progression (KALIE and SHETTY, 2014). It is a proteoglycan present in endothelial cells and in the bloodstream. Patients with untreated acute myeloid leukemia have high levels of endocan in their bloodstream.

Through induction chemotherapy, the amount of leukemic cells is reduced and, consequently, endocan levels decrease, but cases of infection accompanied by neutropenia and problems in bone marrow regeneration increase (HATFIELD, LASSALE, et al., 2013). Cancer patients who have endothelial cell dysfunction may have altered levels of endocan. Low values may suggest an improvement in the maintenance of hematopoiesis. Endocan levels change during bacterial infection processes. Cases of febrile neutropenia are recurrent in sepsis and cancer, several markers have their values altered during this complication, such as tumor necrosis factor and interleukins. These cytokines are responsible for increasing endocan levels through endothelial cells (HATFIELD, LASSALLE, et al., 2013). C-reactive protein (CRP) is another biomarker analyzed in cases of bacterial and viral infection and inflammation. It is a protein produced by the liver and has a plasma half-life of 19 hours. Determining its value during neutropenia cases is advantageous for both the healthcare team and the patient: Studies in neonates and young infants indicate that increases of less than 10mg/L in CRP values collected at 24-hour intervals are useful in excluding the diagnosis of infection and/or suspected sepsis, allowing the discontinuation of antibiotic therapy in selected patients and avoiding the unnecessary use of antibiotics for a longer period. A recent study in septic neonatal patients showed that the serial use of PCR in the first 48 hours of antibiotic therapy can help to predict whether the causative etiologic agent is sensitive to the antibiotic regimen used, being, therefore, a good predictor of the adequacy of empirical antibiotic therapy (LANZIOTTI), PÓVOA, et al.,2016,p.473). C-reactive protein is a marker sensitive to infectious and inflammatory

processes, it is an acute phase protein, its concentration rises when some aggressive agent invades the body, in cases of infection. At plasma concentrations below 10 mg/dL it is considered stable. The main responsible for stimulating the production of c-reactive protein is interleukin 6, which is necessary for the initiation of an effective inflammatory response against infections (RODRIGUES MASSARO, 2013).

Procalcitonin (PCT) is a protein of 116 amino acids, calcitonin propepidium, its production is carried out by the thyroid gland. Serum levels of procalcitonin are directly related to bacterial endotoxin release: Diagnosis of infection is usually based on positive cultures or biomarkers of inflammation; however, culture results can take several days to obtain and these results can be negative in up to a third of cases. In this context, biomarkers are a valuable tool in the early detection of infections. Thus, the greatest utility of PCT in the clinical area is in the diagnosis of sepsis or septic shock (ABRIL, FANDIÑO, et al., p. 134). The determination of procalcitonin levels can influence the patient's antibiotic therapy, reducing or increasing the use of treatment, 20 decreasing the adverse effects of this class of drug and most importantly, preventing the emergence of resistant bacteria. Not to mention that procalcitonin values can eliminate possible cases of sepsis, which is one of the factors responsible for the onset of febrile neutropenia. Values lower than 0.5ng/ml suggest, for the health team, a picture of inflammation, ruling out the presence of microorganisms that cause infections. Values greater than 2.0 ng/ml, the individual may be dealing with possible sepsis. Procalcitonin levels rise faster than C-reactive protein levels. pct values are better for detecting a bacterial infection compared to pcr values (LANZIOTTI, PÓVOA, et al., 2016,p.475 and 476). Chemokines are part of a large family of cytokines that are responsible for a variety of immune responses. They are present in several diseases, including infections and tumor growth (NEUENSCHWANDER, 2009). Alpha chemokines are grouped in the CXC family. This family's main function, in an infectious process, is to stimulate the recruitment of neutrophils. Neutrophils have receptors on their cell surface that are G protein-coupled, such as CXR1 and CXCR2, such receptors are responsible for receiving interleukin 8 (PALOMINO and MARTI, 2015). The treatment of febrile neutropenia requires adequate and early diagnosis. Markers sensitive to infectious processes can help in a better diagnosis and treatment.

FINAL CONSIDERATIONS

Febrile neutropenia is a complication in patients who have cancer and need to undergo treatment with chemotherapeutic substances. Such compounds attack both healthy and diseased cells, damaging the immune system, especially neutrophils that are the target cells of neutropenia. They are responsible for fighting microorganisms through phagocytosis. Chapter one talks about the behavior of these cells against microorganisms and chemotherapeutic compounds. Due to the infectious condition triggered by the decay of neutrophils, the neutropenic patient must make use of antibiotics. The empirical use of these drugs will fight infections and consequently the patient will have a significant improvement. Chapter two deals with these emergency drugs used in cases of neutropenia. The most common clinical symptom of neutropenia is fever. When the patient undergoes blood tests, there is a drop in the number of neutrophils that normally fall due to the use of chemotherapy. Unfortunately, these symptoms do not indicate to the health professional an infection that is more life-

threatening, and it is necessary to study and analyze indicators that change in the face of cases of neutropenia for improvements in the diagnosis of the disease.

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