REVIEW ARTICLE

Sepsis in cancer patients admitted in the ICU: epidemiology, pathophysiology, and biomarkers

Sepse em pacientes oncológicos admitidos em CTI: epidemiologia, fisiopatologia e biomarcadores

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ABSTRACT

Sepsis is one of the main causes of hospitalization in intensive care centers with high rates of morbidity and mortality. Its association with neoplasias has become a highlight due to increased use of propedeutics and interventional therapy that promotes breaking the barriers that protect the host and reduce physical bodily defenses favoring the host invasion by microorganisms. Little is known about these interrelationships. This review off of the MedLine database in interface with Pubmed aims to describe the epidemiology, pathophysiology, and biomarkers in oncology patients admitted in intensive care due to severe sepsis or septic shock. In septic patients without neoplasia, the association of different biomarkers has been the object of study of diagnosis, determination of severity, and outcome. In cancer patients, the biomarkers were primarily used in specific patient subgroups, such as neutropenics, with hematological disease, in order to determine infection. Further studies are required to know how the subgroups of patients with neoplasias behave and to understand and address more appropriately sepsis and septic shock.

Key words: Systemic Inflammatory Response Syndrome; Sepsis; Shock, Septic; Neoplasms; Intensive Care Units.

RESUMO

A sepse constitui-se em um dos principais motivos de internação em centros de terapia intensiva, com altos índices de morbimortalidade. Sua associação com as neoplasias tem se tornado de realce, devido ao aumento do uso de propedêutica e terapêutica intervencionista que propicia ruptura de barreiras que protegem o hospedeiro e reduzem as defesas corpóreas, favorecendo a invasão do hospedeiro por microrganismos. Pouco é conhecido sobre essas inter-relações. Esta revisão da base de dados MedLine interface Pubmed objetiva descrever a epidemiologia, fisiopatologia e biomarcadores em pacientes oncológicos admitidos em terapia intensiva devido a sepse grave ou choque séptico. Em pacientes sépticos sem neoplasia, a associação de diferentes biomarcadores foi objeto de estudo para diagnóstico, determinação de gravidade e desfecho. Nos pacientes oncológicos, os biomarcadores foram principalmente utilizados em subgrupos de pacientes específicos, como neutropênicos, com doença hematológica, com o intuito de determinar a infecção. São necessários mais estudos para conhecer como subgrupos de pacientes com neoplasias se comportam e poder entender e abordar com mais propriedade a sepse e o choque séptico.

Palavras-chave: *Síndrome de Resposta Inflamatória Sistêmica; Sepse; Choque Séptico; Neoplasias; Unidades de Terapia Intensiva.*

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INTRODUCTION

Sepsis is the main reason for hospitalization in the Intensive Care Unit (ICU) and with high morbidity and mortality rate.[1] It is associated with cancer due to several factors such as the therapeutic use of measures that alter body defence barriers against microorganisms, such as chemotherapy and radiotherapy, major surgery, longevity of the cancer population with a high risk of infection, and characteristics of the tumor itself.[2-4]

The inflammatory response triggered by microorganisms in cancer patients is still not well known. Mortality predicting factors such as neutropenia, tumor stage, and use of chemotherapy, seen as negative determinants of prognosis, failed to show a significant association with this outcome.[5-8]

This review aims to contribute to the understanding of how some biomarkers allow the recognition of the epidemiology and pathophysiology of sepsis and septic shock in cancer patients admitted to the ICU.

The MedLine interface PubMed databases were used through the keywords: sepsis, severe sepsis, septic shock, neoplasia, cancer, ICU.

The epidemiology of sepsis in cancer patients

Cancer is the leading cause of mortality worldwide, with 13% of deaths in 2004,[9] with more than 70% of that total in medium or low income countries. [10]Approximately 750,000 annual cases of sepsis occur in the United States, [1] becoming the cause of most of the mortality cases in the ICU.[1,11] Severe sepsis requires ICU admission in more than half of the cases; of these, over 55% have comorbidities[1] and 20% have some neoplasia.[4]

The demographic transition observed in the last decades was associated with increased incidence of sepsis in the elderly considering the aging populations and increased availability of interventional therapies for the treatment of neoplasia.[1] Cancer is associated with sepsis due to multiple factors, especially chemotherapy and radiotherapy, surgery,[2] rupture of mucosal and tegumental barriers, neutropenia, humoral and cellular dysfunction, splenectomy, need for long-term catheters, and local effects of the tumor itself [12] that predispose to more frequent infections.

Patients with neoplasia in any site show an increase of 10% in the possibility of developing sepsis when compared with patients without neoplasia, determining between 2.3 to 25% of all the cases of severe sepsis and septic shock.[9] Hematological neoplasias have a greater possibility of developing sepsis (66.4:1000) than solid neoplasias (7.6:1000), and with increased mortality.[13,14]

In Brazil, some studies have described some clinical relations of sepsis, however, without specific analysis of subgroups of comorbidities.

The BASES study showed an incidence of sepsis of 57 per 1,000 inhabitants, with a higher incidence of neoplasias in groups with infection compared to groups with systemic inflammatory response without infection, 18.3 and 12.1%, respectively.[15]

In 65 ICUs in Brazil, high mortality due to sepsis was detected at 28 days in 2006; 46.6% with description of neoplasia in 14% of the patients, with 8% under immunosuppressive treatment.[16]

The demand for hospitalization in the ICU for patients with neoplasia varied in different studies between 15%[14] and 21.5%[5]; 85% had solid neoplasia and 25% hematological neoplasia; 25% of the solid tumors were metastatic.[14] The length of ICU hospitalization was similar in all studied groups, although this period was longer for those with cancer. The risk of death due to sepsis was increased by 30% in patients with neoplasia representing 10% of all deaths in this group of patients. Among patients with severe sepsis, 13.5% presented some neoplasia with mortality of 37.8%. The increase in incidence of severe sepsis was not related to age unlike in the population without cancer. The incidence of severe sepsis was higher in patients with hematologic diseases than with solid tumors, however, their mortality rate was similar. Hospitalizations due to severe sepsis in cancer patients, regardless of their clinical or a surgical origin, were longer and of high cost compared to the group without cancer.[13] The prevalence of cancer patients in the group with septic shock ranged between 15.3 and 16.9% in France,[17,18] and 25% in the United States.[1]

The epidemiological analysis of septic shock in 22 hospitals in France between 1993 and 2000 revealed that neoplasia (hematologic or solid) occurred in 15.3% and 6.2% of patients with and without septic shock, respectively.[17] In a retrospective study in France, improvement in survival was observed in patients with septic shock and neoplasia when two periods of inclusion of patients, between 1998 and 2001 and 2002 and 2005, were compared. The predicting factors of short-term mortality were: early and adequate start of antibiotic therapy, hyperlactacidemia, creatininemia, need of invasive mechanical ventilation, need for he-

modialysis, and septic shock acquired during hospitalization in the ICU. The evolutive type and form of neoplasia did not relate to the severity but to the number of organs affected and evolution time of dysfunction in the first days of hospitalization.[18]

A prospective and multicentric study in Brazil in 2010 showed that the main reasons for hospitalization were need of postoperative care and sepsis in 57% and 15% of cancer patients, respectively.[5] Another study in Brazil in 2011, including a subgroup of cancer patients diagnosed with sepsis, severe sepsis, and septic shock showed high mortality in the ICU, nursing ward, and at six months in 51%, 65%, and 72% of the patients, respectively. Out of the 563 patients included, 91% had severe sepsis or septic shock. A multivariate analysis showed that disease activity, presence of three to four SIRS criteria, and respiratory, renal, and cardiovascular failure were significantly associated with mortality.[19]

A progressive increase in the incidence of sepsis in patients with neoplasia and under treatment for 23 consecutive years, from 1979 to 2001, was observed with an incidence of 1,465 cases per each 100,000 cancer patients.[2] It is reported that mortality in patients with cancer and septic shock can reach up to 87%.[20]

Mortality prognostic markers have been modified over the last years.[22] Mortality increased with the simultaneity of respiratory or hepatic dysfunction; [21] PCR profile has also been determined as similar in patients with and without neutropenia.[22]

Sepsis pathophysiology

The pathophysiology of sepsis is complex, beginning after exposure to an infectious microorganism. The interaction with the host activates the innate immune system from the recognition of substances in the etiologic agent, called molecular patterns associated with pathogens (PMRPs), which have nonvariable molecular structures that are common to a group of pathogens. Cells identify these PMRPs by means of receptors of pattern recognition (RRP).[23]

Lipopolysaccharides (LPS) from Gram-negative bacteria are the most studied PMRPs. LPS are transferred to CD14 and TLR-4 (Toll-like receptor) receptors through the LPS binding protein known as LPS binding protein (LBP). Other receptors involved in the recognition of pathogens are TLR-2 for the Gram-positive, and TLR-9 and TLR-3 for other microorganisms.[24,25]

After recognition, the activation of different signalling pathways occur culminating in the production of various pro-inflammatory cytokines such as interleukins 1, 2, 6, 8, and 12 and tumor necrosis factors (TNF) α and β. If the patient survives, the release of anti-inflammatory cytokines occurs, especially IL 4, 5, 10, 11, and 13 with the deceleration of the inflammatory response, period known as compensatory anti-inflammatory response syndrome (CARS).[26]

The activation of the adaptive immune system begins with phagocytosis of necrotic cells or bacteria by monocytes/macrophages, differentiation of lymphocytes in Th1, and production of more pro-inflammatory cytokines. The differentiation of lymphocytes into the Th2 phenotype is observed when phagocytosis of apoptotic cells occurs with the production of anti-inflammatory cytokines.[27]

This intricate balance between SIRS and compensatory anti-inflammatory response causes the immune dissonance known as mixed antagonism response syndrome (MARS), determining how sepsis will evolve, either to resolution or death.

Over the past 20 years, more than 70 studies were performed with the aim of preventing the action of these inflammatory mediators in the treatment of sepsis, however, without obtaining an effective response. The only agent approved by the Food and Drug Administration in the past was the activated C protein,[28] used until 2012 and removed from the therapeutic arsenal because of lack of evidence.[29] The use of hydrocortisone was considered beneficial at the beginning of the past decade[30] and later questioned.[31]

Biomarkers in sepsis

Biomarkers represent indicators, measured and evaluated, of some normal biological pathogenic process or response to a particular therapeutic intervention.[32] The diagnosis of sepsis needs better characterization so that it is possible to differentiate severity or comorbidity, determine its clinical manifestations and outcomes, and define specific treatment because patients with infections by the same microorganism develop different pathophysiological responses.

Sepsis triggers the activation of the innate immune system releasing inflammatory and coagulation mediators, which determined the proposal of more than 100 inflammatory biomarkers for its diagnosis.

However, the inflammatory response is a common mechanism to many diseases, not necessarily infectious, and with various manifestations according to various predetermined characteristics in specific groups of patients such as various comorbidities, use of certain drugs, etc.

The production and release of different cytokines occur at high speed, making the determination of absolute values for a certain marker difficult, and very often leading to errors in the definition of studies that aim to treat sepsis, for instance, by means of antagonism to a certain protein.[33]

No biomarker alone is capable of predicting outcomes; however, their association have proved to be more significant.

The behavior of 17 cytokines was analysed in 60 patients with severe sepsis admitted to the ICU of four hospitals in Rio de Janeiro, with mortality of 48.3%; increased concentrations of nine pro- and anti-inflammatory cytokines in patients with septic shock were observed. The ILs 1β, 6, 8, 10; MCP-1 and G-CSF showed a positive correlation with the development of organ dysfunction. The best outcome predictor was MCP-1 in the multivariate analysis.[34]

Significantly reduced values of GM-CSF and MIP-1β were observed on the first day of sepsis in critically ill patients in addition to the increased trend in IL-10 throughout its evolution. The analysis of severity according to the SOFA scale correlated better with the IL-8 and MIP-1β values on the second and third days of evolution, respectively. IL-8 and MIP-1β present significant association with mortality and ROC curve for IL-8 at 0.887 (95% IC = 0.785 – 1.015, p = 0.007).[35]

An association between high levels of IL-6, IL-8, and IL-10 with mortality[36] was detected in severe sepsis and septic shock in those consecutively admitted to the ICU, excluding those under the influence of immunosuppressive therapies.

Sepsis biomarkers in cancer patients

In recent years, better prognosis of severe sepsis and septic shock have been recorded, however, most studies excluded patients with neoplasia due to previous use of drugs that modify the inflammatory response such as corticosteroids and chemotherapy. Mortality significantly reduces when antibiotic therapy,[37] treatments guided by goals,[38] and glycemic control[39] are initiated within the first six hours of the shock treatment,[40] without distinction between subgroups, such as cancer groups.

The inflammatory response in cancer patients is not completely known, with various studies approaching subgroups of patients, such as those with hematological disease, with or without neutropenia, or solid tumors, without obtaining concrete data about the release of inflammatory mediators. The homogenization of these studies in relation to the time of blood sample collection for the evaluation of biomarkers and diagnostic certainty in relation to infection, cause the groups to be very different as in patients without neoplasia. [8]

It is necessary to determine specific patterns of this response in selected groups of patients to guide therapy and determine prognosis and mortality.[41] Lactate, PCT, PCR, and cytokines, as IL [1,6,10] and FNTα, [42] were especially used. The association of various biomarkers allows better prediction. [42-44]

In many studies neutropenia does not reveal an association with mortality. [5-8] PCR as a biomarker in patients with cancer, with or without neutropenia and admitted to the ICU, has more significant value in patients with neutropenia and sepsis and with similar kinetics in these two groups. [22]

The expression of CD11b/CD18 in monocytes has high specificity and sensitivity to define infection in cancer patients, differentiating patients with advanced disease under treatment, and with fever related to cancer. [45]

The value of IL-10 and 12 also possesses good prediction of infection when compared to cancer patients without evidence of infection; in their application, IL-10 is less sensitive than PCT. [46] PCT is a marker of infection induced by exo- or endotoxins and inflammatory cytokines (TNF, IL-2, IL-6). [47] It is elevated in solid neoplasias with bacteraemia and chemotherapy-induced neutropenia when compared to clinical infections and fever of unknown origin. [48] It is useful in determining the prognosis of febrile neutropenic patients without superiority in relation to IL-6 and PCR. [49]

The soluble TREM-1 increases after stimulation with LPS, bacteria, and fungi. [50] In febrile neutropenic patients, bearers of solid or hematological neoplasias undergoing chemotherapy, the elevated values of sTREM-1 are associated with the development of complications, need for hospitalization, and mortality. The same elevation of sTREM-1 is observed in patients with neutropenia regardless of leukopenia

caused by the treatment, and with similar results in relation to PCT. [51]

In 22 patients with different types of cancer, the analysis of IL-6, IL-8, soluble receptor of IL-2, TNF-α, IL-1β, and PCR, in four different stages in the development of neutropenia, before administration of chemotherapy, in the post-chemotherapy afebrile period, in the presence of febrile neutropenia, and in the recovery period revealed that only IL-8 was steadily elevated, however, it failed to discriminate the various risk groups. [52]

The inflammatory response in pigs in septic shock, with and without induced immunosuppression after administration of corticosteroids, cyclophosphamide, and mycophenolate, and after conducting cecal ligation and puncture, is similar dependent on hemodynamic, clinical, and laboratorial variables compared to the control group. Only IL-6 and IL-10 showed significantly elevated values in the immunosuppressed group 24 hours after initiation of the hemodynamic event. [53,54]

The subgroup of cancer patients has not yet benefited from some progresses in the approach of septic patients. The survival of cancer patients admitted to the ICU increased in recent years, [6,53] however, the understanding of the benefit of intensive therapy applied to them is controversial. The progression of neoplasia and response to chemotherapy or radiotherapy does not seem to be associated with increased survival in short-term.[54]

CONCLUSION

This study seeks to describe the various correlations currently recognized as with significance for the understanding of how cancer patients respond to sepsis with the aim to discuss how there can be therapeutic benefits in its approach.

Many studies have already been conducted trying to understand sepsis and its different stages of severity, being epidemiological, pathophysiological, and therapeutic. The diversity of patients included in the same study probably constitutes a factor of difficulty in the understanding of correlations in terms of response to different insults, which vary widely according to the characteristics of each individual. In practice, the knowledge is still insufficient to display benefits regarding the use of measures that would allow improving short-term prognosis and obtaining better quality of life.

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