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Current insights into severe sepsis in cancer patients

Visões atuais a respeito da sepse grave em pacientes com câncer

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CLASSICAL AND EMERGENT RISK FACTORS FOR INFECTIONS

Neutropenia due to myelosuppression by malignant infiltration or that which is more commonly caused by cytotoxic chemotherapy remains the hallmark of immunodeficiency in patients with cancer and is associated with a considerably increased risk for bacterial or fungal infections. In addition to quantitative defects, neutrophils also exhibit various functional defects in chemotaxis, phagocytosis, bactericidal capacity and respiratory burst. The requirements of indwelling long-term central venous access, non-selective cytotoxic activity on dividing cells and poor wound healing account for the frequent impairment in skin and mucosal integrity. Nonetheless, the emergence of new drugs that specifically target lymphocytes has broadened the spectrum of infectious complications to include opportunistic fungal, parasitic and mycobacterial infections, which are observed in patients with lymphoproliferative disorders.[1,2] Interestingly, even a short course of stress-dose corticosteroids that is commonly applied in cases of severe or refractory circulatory failure is likely to increase the risk of intensive care unit (ICU)-acquired infections in hematological patients with septic shock.[3] Most importantly, the spectrum of pathogens responsible for severe infections has changed. Multi-resistant Gram-negative bacteria, especially enterobacteriaceae like *Klebsiella* or *Serratia* spp. together with *Pseudomonas* spp. and others have emerged and exert a major impact on the outcomes of immunocompromised patients for whom any delay in adequate antibiotherapy may be extremely harmful.[4] Extensive prophylaxis with azoles or echinocandins in hematologic patients has led to a shift in the fungal spectrum to more resistant strains and to the emergence of rare fungi.[5]

In addition, some additional risk factors of infections are potentially involved in patients with malignancies. Cancer patients frequently require red blood cell transfusions. Transfusion-related immunomodulation is likely to confer an additional risk of infectious complications, as suggested by a recent meta-analysis of studies that addressed the transfusion thresholds in various populations.[6] Furthermore, some inherited individual predispositions that have been previously described in immunocompetent patients might confer an increased susceptibility to severe infections in immunocompromised patients as well. A deficiency in mannose-binding lectin has thus been associated with a higher incidence of severe bacterial and fungal infections in patients with hematological malignancies. Moreover, functional polymorphisms in TLR4 or long pentraxin PTX3 have been associated with an increased risk of invasive aspergillosis in allogeneic stem cell transplant recipients.[7-9]

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PARTICULARITIES OF SEVERE SEPSIS IN CANCER PATIENTS

It is commonly assumed that the immune pathophysiology of severe sepsis in cancer patients is mostly linked to immune deficiency imposed by anticancer treatments. Recent animal experiments have shed some light on the immunomodulatory impact of an underlying malignancy on the host's response to severe infections. Indeed, mice previously subjected to tumor inoculation displayed an increased mortality to infectious challenges through *P. aeruginosa* pneumonia or polymicrobial peritonitis.[10,11] Changes in the behavior of immune cells, including decreased apoptosis of lymphocytes or expansion of myeloid-derived suppressor cells, are associated with impaired anti-infective responses in hosts with advanced malignant diseases.

Acute circulatory failure is the hallmark of septic shock and involves both macro- and microcirculatory mechanisms. Myocardial systolic or diastolic dysfunction is frequently encountered in cancer patients with septic shock and demonstrates a strong prognostic value in this setting.[12] However, an assessment of the microcirculation in septic patients with neutropenia and thrombocytopenia did not reveal any differences compared with patients with normal blood cell counts.[13]

CURRENT PROGNOSIS

The survival of cancer patients who are admitted to the ICU for severe sepsis has markedly improved over the last several decades and now exceeds 50%, an improvement that has been accompanied by encouraging long-term survival rates and better quality of life.[14] During the late nineties, the 30-day mortality rate of cancer patients who were admitted for septic shock was reported to reach 65% to 72%, whereas subsequent series showed a dramatic relative decline of 25% to 42%.[15,16] A similar trend was observed for patients with neutropenia and severe sepsis for whom in-hospital mortality before and after 2003 dropped from 59% to 43%.[17] Along this line, severe sepsis following chemotherapy that is frequently linked with neutropenia was associated with an in-hospital survival rate of 55%.[18] A volume effect has been demonstrated because survival rates were higher in specialized centers that treat large numbers of patients.[19] The causes of this improvement might include urgent anti-infective measures that were implemented by the combination of broad-spectrum antibiotics with an aminoglycoside as well as early removal of indwelling catheters; another cause may be adhesion to the Surviving Sepsis Campaign guidelines. Generally, early recognition and aggressive management of sepsis are certainly vital to the improvement of patient outcomes.

SEPSIS-LIKE SYNDROMES

Due to the relative uniformity of the inflammatory response, a number of non-infectious acute inflammatory disorders may mimic sepsis in patients with hematological malignancies. Patients with acute monocytic leukemia frequently exhibit pulmonary involvement as a result of leukostasis, pulmonary infiltration and acute lysis pneumopathy.[20] Lymphoma may be revealed by hemophagocytic lymphohistiocytosis.[21] Induction treatments may precipitate tumor lysis syndrome in patients with high-grade hematological malignancies such as acute leukemia, Burkitt lymphoma and anaplastic lymphoma but also rarely in aggressive and bulky solid tumors such as small cell lung carcinoma. In addition to the common metabolic features and acute renal failure, tumor lysis syndrome may result in multiple organ dysfunctions, presumably driven by a massive release of pro-inflammatory cytokines.[22-24] Differentiation syndrome is a particular complication of acute promyelocytic leukemia under induction treatments with all-trans retinoic acid or arsenic trioxide that are likely to induce the overwhelming activation of myeloid cells.[25] Finally, some complications of allogeneic stem cell transplantation, such as sinusoidal obstruction syndrome, engraftment syndrome or graft-versus-host disease may result in systemic inflammatory response and multiple organ dysfunctions.

THE UNDEREVALUATED CONSEQUENCES OF SEPSIS ON CANCER PROGNOSIS

Thus far, studies that have addressed the outcome of severe sepsis in cancer patients have focused primarily on short-term vital status. Few studies have assessed the long-term survival and none have assessed how sepsis and intensive care might impact the prognosis of the malignancy. Intensive care is associated with potentially devastating consequences through profound alterations in functional status or residual organ dysfunctions that may clearly compromise the maintenance of appropriate anticancer treatment in ICU survivors. Furthermore, sepsis is also likely to directly impact tumor growth, although dual pro- and anti-tumoral effects have been reported. On the

one hand, some clinical data suggest that severe bacterial infections may further confer an increased risk of cancer.[26] This particular clinical situation was recently modeled in a double-hit animal model of polymicrobial sepsis followed by tumor inoculation, in which post-septic mice exhibited enhanced tumoral growth compared with control animals with respect to the expansion of regulatory T-cells.[27] On the other hand, some data suggest that a bacterial challenge might act as a vaccine in patients with malignancies. As was recently explained, in 1924, Coley first described a case of remission of sarcoma in a patient who experienced a streptococcal infection and where an injection of a mixture of bacteria was able to induce remission in several patients with malignancies.[28] Furthermore, the modulation of the intestinal microbiota was recently shown to alter tumor growth in mice.[29,30] Whether the frequent exposure to antibiotics might also impact the anti-tumoral response in cancer patients remains to be investigated.

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