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ORIGINAL RESEARCH REPORT

Diagnostic value of sepsis biomarkers in hematopoietic stem cell transplant recipients in a condition of high prevalence of gram-negative pathogens

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Abstract
Objective/background: A decision about the need for antimicrobial therapy in a patient with febrile neutropenia after hematopoietic stem cell transplantation (HSCT) is often complicated because of the low frequency of culture isolation and reduced clinical manifestation of infection. Usefulness and choice of sepsis biomarkers to distinguish bloodstream infection (BSI) from other causes of febrile episode is still argued in HSCT recipients in modern epidemiological situations characterized by the emergence of highly resistant gram-negative microorganisms. In this study a comparative analysis of diagnostic values of presepsin, procalcitonin (PCT), and C-reactive protein (CRP) was performed as sepsis biomarkers in adult patients after HSCT in a condition of high prevalence of gram-negative pathogens.
Methods: A prospective observational clinical study was performed at the Center of Hematology and Bone Marrow Transplantation in Minsk, Republic of Belarus. The biomarkers (presepsin, PCT, and CRP) were assessed in a 4-hour period after the onset of febrile neutropenia episode in adult patients after HSCT. Microbiologically-confirmed BSI caused by a gram-negative pathogen was set as a primary outcome.
Results: Clinical and laboratory data were analyzed in 52 neutropenic patients after HSCT aged 18—79 years. Out of the biomarkers assessed, the best diagnostic value was shown in presepsin (area under the curve [AUC]: 0.889, 95% confidence interval [CI]: 0.644—0.987, $p < .0001$) with 75% sensitivity and 100% specificity, then in PCT (AUC: 0.741, 95% CI: 0.573—0.869, $p = .0037$)

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with 62% sensitivity and 88% specificity. The optimal cut-off value for CRP was set as 165 mg/L, while it had an average diagnostic value (AUC: 0.707, 95% CI: 0.564—0.825, $p = .0049$) with low sensitivity (40%) and should not be routinely recommended as a biomarker in adult patients with suspected BSI after HSCT.

Conclusion: Presepsin may be recommended in adult patients with suspected gram-negative BSI after HSCT as a possible additional supplementary test with a cut-off value of 218 pg/mL. PCT is inferior to presepsin in terms of sensitivity and specificity, but still shows a good quality of diagnostic value with an optimal cut-off value of 1.5 ng/mL. CRP showed an average diagnostic value with low sensitivity (40%) and should not be routinely recommended as a biomarker in adult patients with suspected BSI after HSCT in a condition of high prevalence of gram-negative pathogens.

Introduction

Bacterial bloodstream infections (BSI) are still one the leading causes of infectious complications after hematopoietic stem cell transplantation (HSCT), occurring in approximately 5—10% of autologous and 20—30% of allogeneic HSCT recipients [1]. Despite this, an improved level of supportive care mortality rate due to BSI remains significant, with it being 24—40% in allogenic HSCT [2—6]. Traditional diagnosis of BSI includes results of culturing techniques. Positive blood culture is known to be the most certain method of diagnosis, but it has a number of limitations. For instance, in a large percentage of patients it remains negative despite the typical clinical presentation of sepsis [7]. The other issue of standard culturing techniques is that it still takes significant time for the laboratory to give the results to the doctor. It is well known that the adequate and on-time prescribed antimicrobial therapy is key to success in patients with BSI [8]. But there are a number of cases when it is not clear whether the febrile episode in a concrete patient is a symptom of BSI or if the patient has any other cause (e.g., viral or fungal infection, reaction to chemotherapy infusion, or reactivation of hematologic disease). In patients receiving HSCT the consequences of BSI may be dramatic, taking into account the level of immunosuppression caused by high-dose chemotherapy and total body irradiation. The other issue, which may affect the early diagnosis of BSI in HSCT patients, is the possibility of having a potentially fatal BSI with mild clinical symptoms of infection in such patients; though, the clinical significance of sepsis biomarkers increases in HSCT recipients.

Among the widely used biomarkers which have been studied in neutropenic patients are procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 [9—11]. Despite this fact, the use of biomarkers in neutropenic patients remains a controversial question. For instance, the guidelines of the Infectious Diseases Society of America does not include the use of biomarkers in their recommendations [12]. However, the existing studies are based on small samples of patients receiving HSCT in a total group of neutropenic patients, so there is not enough data to be sure about the diagnostic and clinical significance of those biomarkers in HSCT recipients [13,14]. Previously it was shown that biomarkers are not equally effective in special groups of patients; however, important differences in diagnostic characteristics of presepsin were shown in patients with advanced forms of acute kidney injury and in patients on hemodialysis, which served as a need for different cut-off values in such patients [15,16]. Furthermore, there is no compelling information concerning the usefulness of presepsin in adult patients after HSCT, and there is a practical need for results of a comparative analysis of diagnostic parameters for PCT, CRP, and presepsin in HSCT recipients [17,18]. The continuing emergence of gram-negative pathogens as a cause of BSI affects transplant centers worldwide, so the use of biomarkers in patients after HSCT should be reevaluated according to this recent shift from gram-positive microorganisms [3,19,20]. Therefore, it is important to assess and compare the diagnostic value of presepsin, PCT, and CRP as early biomarkers of a gram-negative bacterial BSI in HSCT recipients.

The main objective of the study was to identify the diagnostic value of presepsin, PCT, and CRP and perform a comparative analysis of those biomarkers in a group of HSCT recipients with gram-negative bacterial BSI.

Methods

Study setting and design

The Republican Center for Hematology and Bone Marrow Transplant is located on the base of the City Clinical Hospital in Minsk, Belarus. The center has more than 150 beds including a Department of Bone Marrow Transplant and Intensive Care Unit for patients with various hematological diseases, with patients preparing and undergoing HSCT. It also includes a microbiology laboratory, laboratory of bone marrow separation and freezing, laboratory of cellular biotechnology, HLA-typing laboratory, and clinical diagnostics laboratory. The study was approved by the Institutional Research Ethics Committee of the hospital, and informed consent was taken from the included patients.

Data relating to age, sex, date, and type of transplantation, conditioning chemotherapy regimen, microorganisms isolated from blood, and antibacterial therapy were prospectively collected in hematopoietic stem cell recipients in this observational clinical study. There were 52 adult patients who had undergone autologous or allogeneic HSCT

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