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Molecular diagnosis of bloodstream infections in onco-haematology patients with PCR/ESI-MS technology

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Summary *Objectives:* Onco-haematological patients are prone to develop infections, and antibiotic prophylaxis may lead to negative blood cultures. Thus, the microbiological diagnosis and subsequent administration of a targeted antimicrobial therapy is often difficult. The goal of this study was to evaluate the usefulness of IRIDICA (PCR/ESI-MS technology) for the molecular diagnosis of bloodstream infections in this patient group.
Methods: A total of 463 whole blood specimens from different sepsis episodes in 429 patients were analysed using the PCR/ESI-MS platform, comparing the results with those of blood culture and other clinically relevant information.
Results: The sensitivity of PCR/ESI-MS by specimen (excluding polymicrobial infections, $n = 25$) in comparison with blood culture was 64.3% overall, 69.0% in oncological patients, and 59.3% in haematological patients. When comparing with a clinical infection criterion, overall sensitivity rose to 74.7%, being higher in oncological patients (80.0%) than in haematological

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patients (67.7%). Thirty-one microorganisms isolated by culture were not detected by IRIDICA, whereas 42 clinically relevant pathogens not isolated by culture were detected moleculary.
Conclusions: PCR/ESI-MS offers a reliable identification of pathogens directly from whole blood. While additional studies are needed to confirm our findings, the system showed a lower sensitivity in onco-haematological patients in comparison with previously reported results in patients from the Intensive Care Unit.

Introduction

Bloodstream infections (BSI) in the immunocompromised patient are a major clinical problem, due to the host's impaired immune system. This state can be caused by their underlying disease (haematological or oncological malignancy), specific therapy of their pathology (steroids, cytotoxic chemotherapy) or several manipulations in the hospital setting (exposure to broad-spectrum antibiotics, nosocomial pathogens or use of catheters). All these factors entail an increased risk for infections.[1,2]

In patients with haematological malignancies or with recent transplantation, corticoids are usually administered. However, corticoid therapy can mask the earliest BSI symptoms, which makes its diagnosis more difficult. Furthermore, the symptoms of infection may be more subtle than in immunocompetent patients due to the severely decreased inflammatory response. Thus, the choice of the most appropriate empirical antibiotic therapy is often challenging in this population. Inadequate antibiotic treatment has been associated with a fivefold reduction in survival.[3] Therefore, achieving a rapid etiologic diagnosis is crucial for the establishment of an appropriate antibiotic treatment and, thus, patient's survival. However, conventional microbiologic methods have a low diagnostic yield, especially in patients undergoing antibiotic treatment; therefore, in numerous cases the etiologic diagnosis is not achieved and the susceptibility to antibiotics is not known.

The PCR/ESI-MS technology, based on broad-range PCR amplification coupled with mass spectrometry, was developed few years ago.[4,5] For the diagnosis of bloodstream infections (comparing with blood culture results plus other microbiological findings), the first version of this technology showed a moderate sensitivity (ranging from 50% to 68%).[6,7] An enhanced sensitivity (up to 83–91%) has been achieved by the latest version, IRIDICA CE-IVD (Ibis Biosciences, Abbott Molecular, Des Plaines, IL), mainly due to an increase in the volume of blood tested (5 mL instead of 1.25 mL in the prior version).[8–11] Given that those previous evaluations had been limited to patients admitted to the Intensive Care Unit (ICU) and the Emergency Room (ER), the goal of this study was to evaluate the usefulness of this platform for the early diagnosis of bloodstream infections in onco-haematological patients.

Materials and methods

Ethics statement

Written informed consent was obtained from all patients or their guardians. This study was approved by the Clinical Research Ethics Committee at Germans Trias i Pujol University Hospital ("Comité Ético de Investigación Clínica", CEIC).

Patients and specimens

This was an observational prospective study including a total of 489 patients with haematological or oncological malignancies either admitted at the Haematology or Oncology Services, or at the Emergency Room at a Spanish tertiary care centre (Fig. 1). All patients had a suspicion of sepsis according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria,[12] and were enrolled between September 2012 and June 2015. At the onset of fever or other clinical signs of sepsis, an extra whole blood specimen was drawn in an EDTA tube (at the same time as the blood culture was inoculated for routine microbiological testing and under aseptic conditions). A sepsis episode was defined as the presence of clinical signs of infection with organ dysfunction with or without a positive blood culture. Sepsis episodes were considered independent when at least one negative blood culture was obtained between them, and/or were caused by different microorganisms, or had a different source. For each patient, only one specimen per sepsis episode was included. The result of the paired blood culture for each specimen was recorded and the leucocyte/neutrophil counts were obtained from the clinical charts (haematology test results from the same day that the blood specimen for IRIDICA testing was drawn). Those patients in which skin contaminants were identified by blood culture were excluded from this study ($n = 18$ cases with microorganisms isolated from a single positive culture bottle with coagulase-negative staphylococci ($n = 9$), *Streptococcus* spp. ($n = 2$), *Corynebacterium* spp. ($n = 3$), *Bacillus* spp. ($n = 1$), *Propionibacterium* spp. ($n = 3$)). Whole blood specimens were stored at −20 °C until testing, according to the IRIDICA Early Access Program protocol.

Conventional microbiological methods

Conventional microbiological methods were performed as previously described.[6,9] Briefly, a set of two blood cultures, including two aerobic and one anaerobic blood culture bottles, were inoculated with up to 10 mL of blood each and were incubated in the Bactec 9240 blood culture system (Becton Dickinson, Franklin Lakes, NJ, USA) for up to 5 days. The Vitek-2 Compact system (BioMérieux, Marseille-L'Étoile, France) was used for the identification and susceptibility testing of the microorganisms directly from positive blood culture bottles.[13,14] Conventional cultures were also performed, following standard microbiological methods