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Impact of antibiotic resistance on outcomes of neutropenic cancer patients with *Pseudomonas aeruginosa* bacteraemia (IRONIC study): study protocol of a retrospective multicentre international study

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ABSTRACT

Introduction *Pseudomonas aeruginosa* (PA) has historically been one of the major causes of severe sepsis and death among neutropenic cancer patients. There has been a recent increase of multidrug-resistant PA (MDRPA) isolates that may determine a worse prognosis, particularly in immunosuppressed patients. The aim of this study is to establish the impact of antibiotic resistance on the outcome of neutropenic onco-haematological patients with PA bacteraemia, and to identify the risk factors for MDRPA bacteraemia and mortality.

Methods and analysis This is a retrospective, observational, multicentre, international study. All episodes of PA bacteraemia occurring in neutropenic onco-haematological patients followed up at the participating centres from 1 January 2006 to 31 May 2018 will be retrospectively reviewed. The primary end point will be overall case-fatality rate within 30 days of onset of PA bacteraemia. The secondary end points will be to describe the following: the incidence and risk factors for multidrug-resistant and extremely drug-resistant PA bacteraemia (by comparing the episodes due to susceptible PA with those produced by MDRPA), the efficacy of ceftolozane/tazobactam, the rates of persistent bacteraemia and bacteraemia relapse and the risk factors for very early (48 hours), early (7 days) and overall (30 days) case-fatality rates.

Ethics and dissemination The Clinical Research Ethics Committee of Bellvitge University Hospital approved the protocol of the study at the primary site. To protect personal privacy, identifying information of each patient in the electronic database will be encrypted. The processing of the patients' personal data collected in the study will comply with the Spanish Data Protection Act of 1998 and with the European Directive on the privacy of data. All data collected, stored and processed will be anonymised. Results will be reported at conferences and in peer-reviewed publications.

Strengths and limitations of this study

- The multicentre design of the study will allow the recording of a large number of episodes.
- The international and multicentre design will provide representative results regarding the current epidemiology of *Pseudomonas aeruginosa* bacteraemia in onco-haematological patients worldwide.
- Information will be provided on risk factors for resistance acquisition and their impact on mortality in the current era of multidrug resistance.
- Due to the retrospective design some information may be lost.
- We may not be able to control for certain measured and unmeasured confounders.

INTRODUCTION

During the last 10 years the aetiology of bloodstream infections (BSI) among neutropenic cancer patients has significantly changed. Several studies have shown an increase of BSI caused by Gram-negative bacilli that may be explained by the use of reduced-intensive chemotherapy regimens, associated to less

severe mucositis, and by the discontinuation of quinolone prophylaxis in some institutions.[1 2]

Pseudomonas aeruginosa (PA) has historically been one of the major causes of severe sepsis and death among neutropenic cancer patients. BSIs due to multidrug-resistant PA (MDRPA) and multidrug-resistant *Enterobacteriaceae* are increasing worldwide and are both associated with poorer outcomes, particularly in immunocompromised patients.[3–5]

There is limited published data describing the characteristics of PA infections in patients with cancer in this era of widespread antimicrobial resistance.[5–7] Moreover, data regarding BSIs in neutropenic patients with solid tumours are particularly scarce.[8] In addition, very little is known about the impact of the introduction of the new broad-spectrum beta-lactam plus beta-lactamase inhibitor combinations (such as ceftolozane/tazobactam) in the therapeutic armamentarium for the treatment of BSI due to MDRPA in neutropenic cancer patients.

Identifying the risk factors for infection due to MDRPA in neutropenic cancer patients could help physicians to recognise patients at risk more rapidly. Therefore, the early administration of a broader empirical antibiotic therapy in these high-risk patients might have a positive influence on their outcomes. In the present international study, we aim to determine the impact of antibiotic resistance on outcomes in neutropenic cancer patients with PA bacteraemia in the current era of widespread antimicrobial resistance, and also to identify predisposing factors for multidrug resistance and mortality. For this purpose, we will compare episodes due to susceptible PA with those produced by MDRPA, and we will compare patients who died with those who survived.

OBJECTIVES OF THE STUDY

Primary objective

- To determine the impact of antibiotic resistance on outcomes in neutropenic cancer patients with PA bacteraemia, measured by all-cause case-fatality rate at 30 days.

Secondary objectives

- To assess the prevalence of multidrug and extremely drug resistance (XDR) among PA isolates causing bacteraemia.
- To identify the risk factors for infection due to multidrug-resistant (MDR) and XDR PA.
- To assess the efficacy of the new beta-lactam ceftolozane/tazobactam for the treatment of bacteraemia due to PA.
- To estimate the cumulative incidence rates of persistent bacteraemia, bacteraemia relapse and other complications at 30 days.
- To identify the risk factors for very early (48 hours), early (7 days) and all-cause (30 days) case-fatality rates.

METHODS AND ANALYSIS

Study design

This is an international, multicentre, retrospective, observational cohort study involving neutropenic cancer patients diagnosed with PA bacteraemia followed up at any of the participating centres during the study period. The study will be conducted in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations (*see research checklist*).[9]

Study population

Data will be collected on all-adult (≥18 years) onco-haematological neutropenic patients diagnosed with at least one episode of PA bacteraemia during the study period.

Study period

Participating centres will retrospectively review all episodes of PA bacteraemia occurring in neutropenic onco-haematological patients from 1 January 2006 to 31 May 2018.

Setting

The study will be conducted at 34 centres from 12 different countries: Spain (14), Turkey (4), Brazil (3), Italy (3), Argentina (2), Germany (2), Chile (1), Colombia (1), Lebanon (1), Slovakia (1), Switzerland (1) and UK (1).

Selection of cases

Patients will be identified from previous retrospective and prospective databases or from the records of the microbiology laboratory at each hospital.

Inclusion criteria

1. Adult patients (≥18 years).
2. Patients diagnosed with a haematological malignancy and/or haematopoietic stem cell transplant recipients, or with solid organ tumour.
3. The presence of neutropenia (<500 neutrophils/mm^3) at the bacteraemia onset.
4. Episodes of monomicrobial PA bacteraemia or polymicrobial bacteraemia in which PA is one of the etiological agents, including community, healthcare and nosocomial infections.
5. Subsequent episodes of PA bacteraemia diagnosed in a patient may be included if the interval between them is 30 days.

Exclusion criteria

Patients with any of the following will be excluded from the study:

1. Unavailability of key data (empirical and targeted therapy and vital status at 30 days).
2. Episodes occurring in non-neutropenic cancer patients.
3. Episodes occurring outside the study period.
4. Age<18 years old.

Data collection

Patients' data will be collected retrospectively. These data will be obtained from various sources, including patients'

electronic records, patients' notes, the hospital laboratory systems and the hospital patient administration system.

The following data will be collected for all cases: sex, age, type of underlying disease and comorbidities, underlying malignancy status, severity of the episode of febrile neutropenia according to the Multinational Association of Supportive Care in Cancer (MASCC) index score,[10] place of acquisition of infection,[11] source of bacteraemia, bacteraemia source control status, clinical and microbiological data, total duration of neutropenia (including days of neutropenia before and after BSI onset), prior therapies received (including antibiotics and immunosuppressive treatments), empirical and definitive antimicrobial therapy, doses and duration of each antibiotic therapy, need for intensive care unit admission and mechanical ventilation, persistent bacteraemia, relapse of bacteraemia, colonisation and/or superinfection by resistant organisms, development of other complications, 48 hours, 7-day and 30-day case-fatality rates.

Patient and public involvement

Patients and public will not be involved in the design or development of the study.

Definitions

Empirical antibiotic therapy: Antimicrobial therapy administered before reception of definitive antibiotic susceptibility results.

Definitive antibiotic therapy: antimicrobial therapy administered according to definitive antibiotic susceptibility results.

Adequate antibiotic therapy: therapy based on at least one in vitro active antibiotic against the PA strain causing the infection. Monotherapy with an active aminoglycoside will be considered adequate.

Persistent bacteraemia: persistent BSI beyond the first 48 hours of adequate antibiotic therapy.

Bacteraemia relapse: relapse of BSI within 7 days of treatment discontinuation.

Microbiological studies

Clinical samples are processed at the microbiology laboratories of each participating centre in accordance with standard operating procedures. PA will be identified using standard microbiological techniques at each centre. In vitro susceptibility is determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.[12] The specific mechanisms of resistance will be provided when possible, according to molecular analyses. Phenotype stratification of PA isolates is made in accordance with recent standard definitions.[13] MDRPA: the isolate is non-susceptible to at least one agent in three or more of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal cephalosporins, antipseudomonal penicillins+beta lactamase-inhibitors, monobactams, fosfomycin, polymyxins. XDR PA: the isolate is non-susceptible to at least one agent in all but two or fewer of the antimicrobial categories listed earlier. PDR PA: the isolate is non-susceptible to all antimicrobial agents listed earlier.

Participant timeline

The follow-up period will last 1 month after bacteraemia onset.

Study outcomes and endpoint assessment

Primary endpoint

- Case-fatality rate at 30 days from onset of bacteraemia.

Secondary endpoints

- 48 hours and 7-day case-fatality rates from onset of bacteraemia.
- Prevalence and risk factors for multidrug and extremely drug resistance acquisition
- Efficacy of ceftolozane/tazobactam for the treatment of bacteraemia due to PA, measured by all-cause (30 days) case-fatality rate.
- Rate of persistent bacteraemia beyond the first 48 hours of adequate antibiotic therapy.
- Rate of bacteraemia relapse within 14 days of treatment discontinuation.
- Rate of other complications within 30 days from bacteraemia onset (eg, ICU admission).

Sample size

The total number of episodes of PA bacteraemia in the participating centres during the study period will determine the sample size. According to the previous experience of each participating centre, we expect to record around 1000 episodes during the study period, allowing the estimation of 95% CIs with a 3% margin of error.

Statistical analysis

Baseline characteristics of participants will be described using mean and SD for continuous variables and frequencies for categorical variables. Cumulative incidence rate will be calculated as the number of events divided by participants at risk at bacteraemia onset. The 95% CI will be estimated using normal approximation for large incidence values (above 10%) and Poisson approximation for small ones. A set of demographic and clinical factors will be analysed to quantify their association with the following outcomes: 30-day mortality, MDR and XDR. To do so, a logistic regression model will be used, and OR with CIs will be presented. Patients' mortality survival functions will be estimated using Kaplan-Meier curves and compared using the log-rank test. Moreover, survival functions will also be analysed at 7, 14 and 30 days. No missing data are expected regarding the main outcomes, since unavailability of related data is an exclusion criterion. With sensitivity purposes, the main analyses will be replicated in patients with high-risk bacteraemia, such as those with pneumonia. Model assumptions, conditions and residuals will be assessed. A p value<0.05 will be considered statistically significant. The analysis will be performed using R software (R V.3.2.5).

Ethical issues

The study has been approved by the *Comité Ético de Investigación Clínica del Hospital Universitari de Bellvitge* (Institutional Review Board of Clinical Research, Bellvitge University Hospital). A list with the participating centres that obtained the approval by their institutional review board, and the centres that did not need the approval is provided in the online Supplementary file 1. To protect personal privacy, identifying information of each patient in the electronic database will be encrypted. The processing of the patients' personal data collected in this study shall comply with the Data Protection Act 1998 and with the European Directive on the privacy of data. All data collected, stored and processed will be anonymised. The investigator/research lead at each site will guarantee that all team members or other persons involved at the site in question will respect the confidentiality of any information concerning the study patients. The Clinical Research Ethics Committee has waived the need for informed consent due to the retrospective nature of the study.

PUBLICATION PLAN

Results will be reported at conferences and in peer-reviewed publications. The first publication will be based on data from all sites, and will be analysed as stipulated in the protocol with supervision by statisticians. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigators and will follow the recommendations of the International Committee of Medical Journal Editors.

DISCUSSION

In recent years, a trend towards an increase of Gram-negative BSI among neutropenic cancer patients has been reported.[1] Neutropenic patients with onco-haematological malignancies are considered a population at high risk for MDR bacterial infections because of their need for long hospitalisation and significant antibiotic pressure.[14] In this regard, recent studies have described an alarming increase in the incidence of bacteraemia due to extended-spectrum beta-lactamase-producing and carbapenem-resistant *Enterobacteriaceae* among neutropenic cancer patients, which may substantially impair patients' outcomes.[2 15 16]

Classically, PA has been one of the leading causes of bacteraemia in neutropenic patients with haematological malignancies and solid tumours, and is associated with poor prognosis.[8 17–19] In recent years, particular attention has been paid to the emergence of MDR *Enterobacteriaceae*, and data on the current epidemiology of PA bacteraemia and the impact of antibiotic resistance in this high-risk population are lacking. The existing literature is based on heterogeneous studies some of which present methodological shortcomings.[5–7 14 20 21]

First, most of the studies have a retrospective and single-centre design.[5 6 14 20 21] Only three prospective studies have addressed this issue and all have a small sample size; in addition, the fact they were conducted more than 7 years ago does not allow the extrapolation of the data to the current era of multidrug resistance.[5 6 16] In addition, the few studies with a multicentre design have included only centres from the same country, and therefore, the results may not be representative of different geographical areas.[3 7] Second, some studies include a diverse variety of infections due to PA, and only a few focus exclusively on patients with PA bacteraemia.[5 7 14 20] Third, only two recent studies describe the current risk factors for MDR-PA acquisition and for mortality in this high-risk population.[7 20] However, one of these studies is a retrospective, single-centre Korean study involving only paediatric patients,[20] and the other is a retrospective, 3-centre study limited to the city of Athens.[7]

The published data comparing the efficacy of combined empirical antibiotic treatment including two active antipseudomonal agents versus monotherapy in patients with febrile neutropenia are controversial. The aim of empirical combination therapy is to provide extended-spectrum coverage against MDR organisms in high-risk patients, since a delayed initiation of adequate antibiotic treatment has been associated with poorer outcomes, particularly in patients with PA bacteraemia.[5 7 20 21] However, an important meta-analysis published in 2013 was unable to show any advantage of combination antibiotic treatment in cancer patients with neutropenia.[22] Nonetheless, in a recently published report, Tofas *et al* found a trend towards improved survival with combination therapy in this setting.[7] Clearly, more studies are needed to analyse whether combination therapy could be beneficial in the current era of multidrug resistance.

Clinical experience with the use of new broad-spectrum beta-lactams to treat MDR-PA infections, such as ceftolozane/tazobactam, is gradually accumulating in the general population. However, little is known about its use for the treatment of MDR-PA bacteraemia in neutropenic cancer patients.

The present study aims to identify the current impact of the antibiotic resistance on outcomes in neutropenic patients with PA bacteraemia, and to determine the risk factors associated with multidrug resistance and mortality. We will also assess the efficacy of new broad-spectrum beta-lactams against MDR-PA strains, since alternative treatments are urgently needed in this vulnerable population. This study shall provide useful information for physicians' daily clinical practice, who need to rapidly identify patients at high risk for MDR-PA bacteraemia, to be able to promptly initiate effective antimicrobial therapy and improve patients' outcomes.

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Contributor All authors were involved in the study concept. AA-P, CG, RP and JC were involved in the design of the study. CT was responsible for the elaboration of the statistical analysis plan. DT was responsible for the elaboration of the online database. AA-P, MA, RA, AB, A-SB, SC, LD, EG, PH, FH, K-YI, BI, SK, WK, GMa-Ca, AM, JIM, IM-G, PM-D, MMi, MMo, HMPM, IM, AN, CO, MP, JLDP, PP-A, IR-C, ORS, RT, LY, MZRG, GC, FE-V, MRA, CMA, JM, OG, P-YB, OM, SEZ, J-FJ, HB, GP-H, ML, JMA, BP, JF, GM, LM, RC, LL-S, JPH, MHM, MC, JR-B, RG, PC, MB, NC, PSA, CC, CG-V, JA-C,

NL, AU-O, AN-Z, LCC, WVF and AASM were responsible for the data collection and introduction in the online database. FTu was responsible for the microbiological supervision of the study. AA-P, CG, CT and JC drafted and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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