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Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients

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ABSTRACT

Objectives: The primary objective was to describe clinical features, treatment and outcomes in patients with carbapenemase-producing Enterobacteriaceae (CPE) bacteremia. Additionally, patients treated with ceftazidime/avibactam (study group) were compared to the rest of the patients (comparator group) to determine the influence of the treatment in both crude mortality and clinical cure.
Methods: Multicenter and retrospective study that included patients with hematologic malignancies who had CPE bacteremia. A bivariate analysis was performed to compare the clinical variables between the study group and the control group.
Results: 31 patients were included. Bacteremia was considered primary in 14 (45%) patients. Overall crude mortality at 30 days was 45.2% (n = 14). Mortality was more frequent when septic shock (78.6% vs 11.8%; p > 0.001) and higher Pitt score (6 + 14 vs 1.5 + 4; p < 0.01) were present. 8 patients (25.8%) received treatment with ceftazidime/avibactam. No significant differences in crude mortality were found between study and comparator groups ($p = 0.19$). In contrast, patients in study group had higher clinical cure rates than the comparator group within 14 days of initiating treatment (85.7% vs. 34.8%, respectively, $p = 0.031$).
Conclusions: CPE bacteremia is associated with high mortality in patients with hematologic malignancies. Ceftazidime/avibactam may be an effective alternative for treating these patients.

Introduction

Patients with hematologic malignancies are at high risk of Enterobacteriaceae bacteremias. In these patients, beta-lactams are widely used for the treatment of these infections (Freifeld and Bow, 2011). However, the increase in the incidence of carbapenemase-producing Enterobacteriaceae (CPE) infections may heighten the risk of treatment failure (Satlin et al., 2013; Hirsch and Tam, 2010). New antibiotics are therefore necessary for the treatment of these infections.

Ceftazidime/avibactam is a novel combination of β-lactam/β-lactamase inhibitor that exhibits activity against class A (such as ESBLs, *Klebsiella pneumoniae* carbapenemases), class C (AmpC) and some class D (OXA) β-lactamases (Shields and Clancy, 2015; de Jonge et al., 2016). It is not active against metallo-β-lactamase producers (Hackel et al., 2016). Our objective was to study whether treatment with ceftazidime/avibactam decreases crude mortality at 30 days in patients with hematologic malignancies or aplastic anaemia with CPE bacteremia.

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Materials and methods

Study design and setting

This multicenter, retrospective, and observational study included consecutive patients with hematologic malignancies who presented with CPE bacteremia from June 2012 to March 2016. The patients were recruited from three centers in Spain and one in Israel.

Inclusion and exclusion criteria

The inclusion criteria were: i) age >18 years; ii) initiation of empirical treatment within the first 24 hours after blood culture collection (considered day 1); and iii) initiation of targeted treatment within the first 7 days after blood culture collection. Patients who did not receive antibiotic treatment for at least 48 hours and those with polymicrobial bacteremia were excluded.

Definitions

Bacteremia was defined as the isolation of CPE in blood cultures. Treatment was considered as empirical when administered prior to the availability of susceptibility tests and as targeted once the results of the susceptibility tests were available.

Antibiotics were included in the therapeutic regimen according to the clinical judgment of the attending physician. To assign patients to a given therapeutic regimen (both empirical and targeted), the duration of the treatment had to be at least 48 hours, except in patients that died before that time, who were included if they had received at least 24 hours of treatment. The association of $\geq$2 *in vitro* active antibiotics was considered combination treatment. Administration of at least one antibiotic with *in vitro* susceptibility was considered appropriate treatment. Carbapenems were considered active if the minimum inhibitory concentration (MIC) was $\leq$8 mcg/mL. Tigecycline was considered inactive in bacteremias of urinary origin.

The primary endpoint was to describe clinical features, treatment and outcomes in patients with CPE bacteremia. Moreover, a comparison between patients treated with ceftazidime/avibactam (study group) and patients who received other antibiotics (comparator group) was performed in order to evaluate differences in: i) crude mortality at 30 days from the day the blood cultures were taken, and ii) clinical cure (resolution of all signs and symptoms of infection) at 14 days after the onset of antibiotic treatment.

The site of the bacteremia was determined according to the criteria of the Centers for Disease Control and Prevention (CDC) (Horan et al., 2008). Ceftazidime/avibactam was administered intravenously at the standard dose of 2/0.5 grams every 8 hours. The dose was adjusted in cases of renal failure according to the manufacturer's instructions (Acycaz (Ceftazidime-avibactam), 2016).

CPE was defined according to CDC criteria (Center for Disease Control and Prevention - Healthcare-associated Infections (HAIs)). CPE was identified and susceptibility studies were performed in the microbiology laboratory of each center using the EUCAST cut-off points. Carbapenemases were detected phenotypically and confirmed by polymerase chain reaction (PCR) according to the standards of each local Microbiology laboratory.

Statistical analysis

Univariate analysis was performed to compare the patients in the study group versus those in the comparator group and to identify factors related to mortality. Fisher's exact test was used for categorical variables and the Mann-Whitney U-test for continuous variables. Statistical significance was defined as $p < 0.05$. The statistical analysis was performed using the SPSS statistical package version 15.0 (Chicago, IL, USA).

Table 1
Characteristics of patients with bacteremia caused by carbapenemase-producing Enterobacteriaceae.

Characteristics	Total (N=31)	Ceftazidime-Avibactam (N=8)	Other treatments (N=23)	p value
Hospital				
H Reina Sofía	8 (25.8%)	2 (25%)	6 (26.1%)	
H Ramón y Cajal	6 (19.4%)	2 (25%)	4 (17.4%)	
H La Paz	15 (48.4%)	4 (50%)	11 (47.8%)	
H Tel Aviv	2 (6.5%)	0 (0%)	2 (8.7%)	
Sex, Male	19 (61.3%)	4 (50%)	15 (65.2%)	0.67[b]
Age	59 ± 60[a]	61 ± 42[a]	59 ± 59[a]	0.63[c]
Hematologic disease				
Aplastic anemia	1 (3.2%)	0 (0%)	1 (4.3%)	1.00[b]
Acute leukemia	15 (48.4%)	3 (37.5%)	12 (52.2%)	0.68[b]
Multiple myeloma	2 (6.5%)	1 (12.5%)	1 (4.3%)	0.45[b]
Lymphoma	11 (35.5%)	3 (37.5%)	8 (34.8%)	1.00[b]
MDS	1 (3.2%)	0 (0%)	1 (4.3%)	1.00[b]
MPD	1 (3.2%)	1 (12.5%)	0 (0%)	0.25[b]
Comorbidities				
Diabetes	4 (12.9%)	0 (0%)	4 (17.4%)	0.55[b]
COPD	6 (19.4%)	0 (0%)	6 (26.1%)	0.29[b]
CRF	2 (6.5%)	2 (25%)	0 (0%)	0.06[b]
Heart failure	4 (12.9%)	2 (25%)	2 (8.7%)	0.26[b]
Microorganism				
K. pneumoniae	25 (80.6%)	6 (75%)	19 (82.6%)	1.00[b]
S. marcescens	2 (6.4%)	0 (0%)	2 (8.7%)	1.00[b]
E. cloacae	1 (3.2%)	0 (0%)	1 (4.3%)	1.00[b]
K. oxytoca	2 (6.4%)	1 (12.5%)	1 (4.3%)	0.41[b]
E. coli	1 (3.2%)	1 (12.5%)	0 (0%)	0.25[b]
Type of carbapenemase				
OXA 48	19 (61.3%)	5 (62.5%)	14 (60.8%)	1.00[b]
KPC	12 (38.7%)	3 (37.5%)	9 (40.9%)	1.00[b]