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BRIEF REPORT

Ertapenem plus meropenem combination treatment in carbapenem-resistant *Klebsiella pneumoniae* bacteremia: an analysis of 53 cases

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Abstract

Herein, we aimed to describe the outcomes of patients with blood stream infections due to carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) who received ertapenem plus meropenem combination treatment (EMCT). A total of 53 patients with culture proven CR-Kp bacteremia treated with ertapenem + meropenem were included. The patients with secondary bacteremia due to urinary tract infection exhibited a significantly lower 1-month mortality (OMM), particularly in those with microbiological eradication and those with end-of-treatment success. Salvage EMCT resulted in 49% 1-month survival.

Keywords Double carbapenem therapy · Carbapenem-resistant *Klebsiella pneumonia* · Bacteremia

Introduction

Treatment options for carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) are severely limited. According to the latest guidelines, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol can be used to treat CR-Kp infections [1]. On the other hand, in many countries or hospitals, access to and/or reimbursement for these drugs is extremely limited.

Several clinical studies have investigated the efficacy of double carbapenem therapy for CR-Kp infections [2–4]. However, there are very few well defined studies on the treatment of CR-Kp bacteremia and further studies are needed [5]. In this retrospective cohort study, we

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aimed to contribute to the literature by describing the outcomes of patients with bloodstream infections with CR-Kp who received ertapenem plus meropenem combination treatment (EMCT).

Methods

This study was conducted at a tertiary-care university hospital. All patients who fulfilled the following three criteria were included in the study: (i) adult patients (>18 years old) who were consulted by Infectious Diseases consultants between August 2016 and September 2022, (ii) had culture-proven CR-Kp bloodstream infection, and (iii) were treated with EMCT regimens.

Bloodstream infection or bacteremia was defined as the presence of a microbial pathogen in blood culture due to infection, not specimen contamination [6].

Microbiological analysis

Antibiotic sensitivity tests were performed using the VITEK2 (BioMerieux, France) system and evaluated according to EUCAST criteria [3]. Carbapenem MIC (minimum inhibitory concentration) levels were determined by gradient test (BioMerieux, France) on Mueller Hinton agars.

Evaluation of response definitions

Microbiological success was defined as the clearance of the infecting bacteria in the test of cure cultures. End-of-therapy (EOT) clinical success was defined as a persistent response in clinical signs (including fever and symptoms), with no indication of additional antibiotic therapy other than the ones initiated with EMCT, and/or negative culture reported at the end of the therapy.

Statistical analysis

Statistical analysis was performed using the chi-squared and Student's *t*-test. A *p*-value less than 0.05 was considered significant.

Ethical approval

This study was approved by the local Institutional Review Board (21-6.1 T/63 on June 25, 2021).

Results

There were a total of 53 cases fulfilling the study inclusion criteria. Mean durations of hospitalization and EMCT were 39.6 ± 3.3 and 17.3 ± 1.2 days, respectively.

All isolates were resistant to ertapenem (MIC level >0.5 mg/L). All isolates were resistant to meropenem, except three (6%) with intermediate susceptibility (meropenem MIC 2–8 mg/L). All isolates were resistant to imipenem, except two (4%) with intermediate susceptibility (imipenem MIC 4 mg/L).

All cases received EMCT. Following culture results, EMCT was combined with colistin in 20 cases (37.7%), tigecycline in 19 cases (35.8%), an aminoglycoside in 6 cases (11.3%), and fosfomycin in 6 cases (11.3%). Additionally, 19 cases (35.8%) received EMCT alone.

The overall clinical success rate at the EOT was 51%, while the overall 1-month mortality (OMM) rate was 51%. The OMM rate was found to be significantly lower in patients who achieved EOT clinical success (7.4% vs. 96.2%, $p < 0.001$). Additionally, there was significantly lower OMM in the subgroup of patients with bacteremia and urinary tract infections (Table 1; $p = 0.002$). During the follow-up period, seven relapses and seven reinfections were recorded. In the overall cohort, the OMM rate was 11/12 (92%) in cases with no microbiological eradication, compared to 32% (12/37) in the microbiological eradication subgroup ($p < 0.001$). When we further analysed the combination treatment in terms of the sensitivity of the combination antibiotic (sensitive vs. intermediately resistant), the microbiological eradication rate was similar in both groups (15/21 vs. 22/28, $p = 0.565$).

None of the specified antibiotic regimens, including only EMCT vs. others, resulted in a statistically significant difference in terms of OMM. In the overall cohort, 9 out of 25 (36%) cases in which there was no switch of the antimicrobial treatment resulted in death during the first month. The mortality rate was 58% (14/45) in patients whose antimicrobial treatments were revised ($p = 0.117$). Eight patients required vasopressor treatment during the initiation of EMCT, and there was no significant difference in terms of OMM between this group and the others (5/8 vs. 22/45, $p = 0.704$).

There was no severe adverse effect that required withholding the EMCT.

Discussion

CR-Kp infections pose significant health risks worldwide. Although treatment guidelines recommend new antibiotics such as ceftazidime-avibactam, meropenem-vaborbactam, or cefiderocol for treating carbapenem-resistant

Table 1 Analysis of study variables in terms of one month mortality (*p* values show comparison of that regimen versus others)

Treatment regimens after culture results		Day-30 mortality		*p* value
		Present	Absent	
Gender	Female	8 (62%)	5 (38%)	0.379
	Male	19 (52%)	21 (48%)	
Age (years)		62.19 ± 2.76	58.92 ± 2.91	0.420
Day 3–5 microbiological success	Present	4 (20%)	16 (80%)	0.002*
	Absent	19 (65%)	10 (35%)	
End of treatment microbiological success	Present	12(32%)	25 (68%)	< 0.001*
	Absent	11 (92%)	1 (8%)	
Pneumonia subgroup	Present	7 (70%)	3 (30%)	0.293
	Absent	20 (46%)	23 (54%)	
Urinary tract infection subgroup	Present	0 (0%)	8 (100%)	0.002*
	Absent	27 (60%)	18 (40%)	
Only receiving EMCT	Present	7 (37%)	12 (63%)	0.920
	Absent	13 (38%)	21 (62%)	
End of therapy clinical success	Present	2 (7%)	25 (93%)	< 0.001*
	Absent	25 (96%)	1 (4%)	

**p<0.05*

Enterobacterales (CRE) infections, these agents were not available in our country during the study period [7]. Furthermore, meropenem-vaborbactam or cefiderocol is still not available in our country. Ceftazidime-avibactam reimbursement was available only between April 2021 and August 2022 and only for ICU cases and strains with concomitant amikacin and gentamicin resistance [8]. Notably, 26.2% of 140 clinical CRE strains isolated between January and August 2021 in our setting exhibited resistance to ceftazidime-avibactam [9]. As a result, a double carbapenem strategy was chosen as a salvage therapy approach in the presented cases.

Though data related to bacteremia is quite rare, double carbapenem strategy has important in vitro and in vivo rationale. Venugopalan et al. conducted a study involving 36 patients with CR-Kp bacteremia to compare the efficacy of conventional therapy (doripenem plus colistin) to double carbapenem therapy (doripenem plus ertapenem). They found that clinical cure was achieved in 72% of patients treated with double carbapenem therapy, compared to only 39% of patients treated with colistin ($p = 0.0489$). Additionally, the double carbapenem group had a higher microbiologic eradication rate with 94% of patients achieving success, compared to only 71% in the conventional therapy group ($p = 0.1147$) [10]. In a study by Souli et al., 27 patients with complicated urinary tract infections, with or without secondary bacteraemia ($n = 4$ and $n = 12$), primary infections ($n = 6$), or catheter-related bloodstream infections ($n = 2$) were treated with a double carbapenem (meropenem plus ertapenem) therapy as salvage therapy for infections caused by KPC-2-producing Kp. The results showed a 77.8% clinical and 74.1% microbiological success rate, with 29.6% crude in-hospital mortality (18.5% day 28 mortality) and 11.1% attributable mortality [11].

Cprek et al. also investigated patients with CR-Kp infections who received EMCT. They found a clinical success rate of 43% (3/7) for patients with bloodstream infections and 67% (2/3) for patients with urinary tract infections. Additionally, all cases treated for bloodstream or urinary tract infections achieved microbiologic success (7/7 and 3/3, respectively). The 30-day mortality rate was 14% (1/7) in patients with bacteremia and 0% in patients with urinary tract infection [12]. In our study, we discovered that overall OMM was as high as 51%. As expected, compared to other cases, OMM was lower in cases with microbiological eradication and EOT success ($p < 0.001$). Additionally, our findings align with existing literature as we observed no OMM in the subgroup of patients with urinary tract infection and bacteremia.

Although we were unable to perform a molecular epidemiology in the study CR-Kp strains, a multicentre study conducted between 2017 and 2018 in our country found that OXA-48 was the most common type of carbapenemase produced by *K. pneumoniae* bloodstream isolates (92/131, 70.9%), followed by NDM (20.6%) and KPC (15.2%) [13]. An in vitro study evaluated the effectiveness of meropenem and ertapenem combination against CR-Kp, showing an enhanced effect of the combination, especially against OXA-48 producing Kp isolates (1/10 KPC-2, 4/7 OXA-48, 2/7 NDM, and 0/3 NDM-1+OXA-48 producers) at 24 h [14]. A retrospective cohort study in another OXA-48 endemic setting from our country revealed that inappropriate therapy (aOR 4.65, 95%CI 1.50–14.40, $p = 0.008$) and 14–day clinical failure (aOR 3.14, 95%CI

1.09–9.02, p = 0.033) were associated with 30-day mortality in patients with CR-Kp bloodstream infections [15].

Research findings about CR-Kp infections, have important regional differences in terms of clinical outcomes such as OMM which was reported lower in China (12%) than in the USA (23%) and South America (28%) in a multicentre, prospective, cohort study. Therefore, results from one country might not be generalizable due to patients' and bacterial characteristics, resistance patterns, as well as the antibacterial arsenal in that particular country [16]. The relatively high OMM in our cohort may be due to the fact that most of the strains had no other beta-lactam treatment option and all cases had confirmed bacteremia.

Our study has a several limitations, including its retrospective design (which is why control cultures were available for some of the patients) with limited number of patients. Additionally, we were unable to determine the types of carbapenemases in the CR-Kp strains. Another disadvantage was the use of an automated system (VITEK) for tigecycline and colistin susceptibility data. However, it is worth noting that to our knowledge, this is the largest CR-Kp bacteremia series in the literature treated with DCT.

In conclusion, although high OMM rates, which were not very impressive, were observed with EMCT in patients with bacteremia caused by CR-Kp, none of the patients with UTI + bacteremia had OMM. In our cohort, lack of microbiological success and EOT success was associated with increased OMM. We believe that these results are particularly important for resource-limited settings by providing evidence that EMCT can be used as a salvage therapy option in treating CR-Kp infections. We suggest further investigations including randomized controlled studies regarding the subject.

Author contribution Author UÖ and author ORS have given substantial contributions to the conception or the design of the manuscript; author UÖ, DA, AK, DB, BK, GŞ, AUÖ, CBA, MM, and SM to acquisition, analysis and interpretation of the data; and author ORS revised it critically.

Data availability The data that support the findings of this study are not publicly available but can be provided with request from the corresponding author, UÖ.

Code availability None available.

Declarations

Ethics approval This study was approved by the local Institutional Review Board (21-6.1 T/63 on June 25, 2021).

Consent to participate All authors have participated to drafting the manuscript.

Consent for publication All authors read and approved the final version of the manuscript.

Competing interests The authors declare no competing interests.

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