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BRIEF REPORT

Pharmacodynamic target attainment of the synergism of ceftazidime-avibactam in combination with amikacin against OXA-producing extensively drug-resistant or pan drug-resistant (XDR/PDR) *Pseudomonas aeruginosa*

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Abstract
To investigate the pharmacodynamic target attainment of ceftazidime-avibactam (CZA) in combination with amikacin against OXA-producing extensively drug-resistant/ pan-drug-resistant *Pseudomonas aeruginosa* (XDR/PDR-PA). The minimum inhibitory concentrations (MICs) of CZA and amikacin against OXA-producing XDR/PDR-PA were determined by the checkerboard method, and the combined inhibitory index (FICI) was calculated to evaluate whether the combination of the two antimicrobials has a synergistic effect on OXA-producing XDR/PDR-PA in vitro. The pharmacokinetic (PK) and pharmacodynamic (PD) parameters of CZA and amikacin were combined by Monte Carlo simulation (MCS) to evaluate the cumulative fraction of response (CFR) of the two antimicrobials for the treatment of OXA-producing XDR/PDR-PA infection. The results of synergy tests of CZA in combination with amikacin suggested that 77.3% of XDR/PDR-PA showed synergistic effects. When the PK/PD target was greater than 50, CFR was 97.84% for CZA 2.5 g q8h when CZA in combination with amikacin. CZA in combination with AMK has a synergistic effect in vitro and could be a potential option for treating OXA-producing XDR/PDR-PA infections.

Keywords Ceftazidime-Avibactam · Extensively drug-resistant/pan-drug-resistant *Pseudomonas aeruginosa* · Synergy tests · PK/PD

Introduction

In recent years, extensively drug-resistant or pan-drug-resistant *Pseudomonas aeruginosa* (XDR/PDR-PA) has become widespread worldwide [1]. CHINET surveillance of antimicrobial resistance among bacterial isolates in 2022 showed that 22.4% (6109/27257) of the 27,257 *P. aeruginosa* strains collected were resistant to carbapenems. Numerous clinical studies have reported that "high-risk" *P. aeruginosa* clones, such as ST235, ST357, and ST244, have spread globally [2]. The spread of these high-risk strains poses a significant threat and challenge to the global public [3].

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Infections caused by XDR/PDR-PA result in prolonged hospitalization, rising mortality, and increased medical costs [4, 5]. Therefore, the rapid and effective treatment of infections caused by XDR/PDR-PA has become a severe problem for doctors in all departments [6]. Because of a lack of appropriate treatment options, infections caused by XDR/PDR-PA present a significant threat to morbidity and mortality worldwide. Therefore, the development of new antimicrobial drugs and the optimal use of existing antimicrobial drugs could be a solution to this problem.

Ceftazidime-avibactam (CZA) was approved by the FDA in 2015 for treating multidrug-resistant gram-negative bacterial infections and is now more widely used in clinical practice [7]. As an aminoglycoside, amikacin may cause ototoxicity, nephrotoxicity, and neuromuscular blockade with irrational dosing [8]. Current in vitro experiments have demonstrated that CZA combined with amikacin has synergistic or additive effects on XDR-PA [9]. However, there is no relevant literature on the pharmacodynamic attainment of

the synergism of CZA in combination with amikacin against XDR/PDR-PA.

Based on the above research background, this paper conducted in vitro antimicrobial susceptibility tests and synergy experiments using CZA and amikacin on 22 OXA-producing XDR/PDR-PA. According to the PK/PD model of CZA and amikacin, the pharmacodynamic target attainment of the synergism of CZA in combination with amikacin against OXA-producing XDR/PDR-PA was explored.

Methods

Bacterial strains and antimicrobial agents

Our team collected 22 non-duplicated XDR/PDR *P. aeruginosa* from sputum and tracheal aspirate samples of critically ill patients with lower respiratory tract infections (i.e., bronchitis and pneumonia) in the first Medical Center of Chinese People's Liberation Army General Hospital from January 2016 to November 2021. Each *P. aeruginosa* were resistant to imipenem (≥ 16 mg/L), meropenem (≥ 16 mg/L), aztreonam (≥ 32 mg/L), levofloxacin (≥ 8 mg/L), ciprofloxacin (≥ 4 mg/L), gentamycin (≥ 16 mg/L), tobramycin (≥ 16 mg/L), piperacillin (≥ 128 mg/L), piperacillin-tazobactam (≥ 128 mg/L), ceftazidime (≥ 64 mg/L) and cefazolin (≥ 64 mg/L). All strains were identified by VITEK®2 system (bioMérieux, Marcy-l'Étoile, France). CZA and amikacin standards were purchased from MedChemExpress.

Whole-genome sequencing

Illumina MiSeq short-read sequencing (Illumina, San Diego, CA, USA) was used to sequence the whole genome of 22 strains of XDR/PDR-*P. aeruginosa*. Subsequently, we applied the Comprehensive Antibiotic Resistance Database v.1.2.0 (McMaster University, Hamilton, Ontario) to analyze the resistance genes of each strain.

Antimicrobial susceptibility testing

A two-fold dilution method determined the minimum inhibitory concentrations (MICs) of CZA and amikacin. The definition of MICs was the lowest antibiotic concentration that inhibits the growth of bacteria in the culture medium after 18 to 24 h of in vitro. Quality control strains of each batch of susceptibility tests were *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 (American Type Culture Collection, Manassas, VA, USA). Besides, all antimicrobial susceptibility tests were conducted three times, and all results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI). The breakpoints of CZA and amikacin against *P. aeruginosa* are 8/4 mg/L and 16 mg/L, respectively.

Synergy testing with the checkerboard method

The checkerboard method assessed the synergy test of CZA combination with amikacin against *P. aeruginosa*. In brief, a 96-well microdilution plate containing a series of twofold concentration increments of CZA and amikacin was prepared. $5*10^5$ CFU/ml of bacterial cells were dispensed in each well and incubated at 37 °C for 20 h. The concentration of CZA and amikacin ranged from 0.25 mg/L to 256 mg/L and 4 mg/L to 128 mg/L, respectively. The fractional inhibitory concentration index (FICI) was used to assess the synergistic effect of CZA and amikacin. FICI = (MIC of CZA in the combination/MIC of CZA alone) + (MIC of amikacin in the combination/MIC of amikacin alone). When FICI < 1, the combination of two drugs is considered to have a synergistic effect. 0.5 < FICI < 1 means partial synergism, an FICI = 1 means additivity. Besides, 1 < FICI < 4 means indifference, and an FICI > 4 means antagonism. The Loewe additivity method was used to analyze the results of synergy tests. The equation of Loewe additivity index (α) is $1 = \mathrm{FICI} + \alpha$. α=0 indicates additivity, α>0 indicates synergistic and α<0 indicates antagonistic [10].

Monte Carlo simulation

PK parameters of ceftazidime, avibactam, and amikacin were obtained from previously published papers, shown in Table S1 [11, 12]. As for ceftazidime, 50%*f*T > MIC and 50%*f*T > 5 × MIC were considered the best indication for assessing BSIs and LRTIs, respectively [13, 14]. When combined with ceftazidime, %50*f*T > CT of 1 mg/L was considered the PK/PD target of avibactam [15, 16]. If the simulated value failed to meet the concentration threshold, we set ceftazidime 50%*f*T > MIC to 0. The $\%fT > 5 \times MIC$ was calculated using the following equation:

$$\%fT < 5 \times MIC = [T_{\mathrm{inf}} - \frac{V_{\mathrm{d}}}{CL} \times Ln(\frac{R_0/CL}{R_0/CL - 5 \times MIC}) + \frac{V_{\mathrm{d}}}{CL} \times Ln(\frac{R_0/CL - R_0/CL \times \mathrm{e}^{-CLT_{\mathrm{inf}}/V_{\mathrm{d}}}}{5 \times MIC})] \times \frac{100}{DI}$$

In this equation, R_0 = total-dose × $f/T_{\inf}$. f means the fraction of free drug in the plasma, DI (h) represents the dosing interval, $T_{\inf}$ (h) represents the infusion time, Ln represents the natural logarithm. As for AMK, the PK/PD target was C_{max}/MIC > 8 [17]. The C_{max} was calculated using the following equation: $Cmax\left(\frac{mg}{L}\right) = \frac{D/T\times(1-e^{-\frac{CL}{Vd}\times T})}{Vd\times CL/Vd\times\ (1-e^{-\frac{CL}{Vd}\times\tau})}$. In this equation, D (mg) means the total dose and T (h) means the duration of infusion. CL means the clearance. Vd (L) represents the volume of distribution. τ (h) means the dosing interval. The dosing regimen for CZA is 2.5 g q8h. When combined with CZA, the dosing regimen for AMK is 25 mg/kg.

Oracle Crystal Ball software (version 11.1.24) was used to conduct simulations based on 10000 patients to evaluate the efficacy of CZA or AMK monotherapy and combination therapy. Meanwhile, Monte Carlo simulations were used to integrate the PK and PD parameters [18, 19]. PK parameters were followed by log-normal distributions. The distributions of MICs were used with a uniform distribution. For each CAZ dosage regimen, the probability of target attainment (PTA) was defined by counting the subjects who reached a 50%fT > n × MIC. For each AMK dosage regimen, the PTA was defined by counting the subjects who reached a C_{max}/MIC > 8. The cumulative fraction of response (CFR) was calculated using the following equation:$CFR = \sum_{i=1}^{n} PTA(MICi) \times p(MICi)$. MICi is determined based on each MIC value and $p(MICi)$ indicates the percentage of strains with that MIC [19].

Results

β-lactamase genes of 22 XDR/PDR-PA

Based on whole genome sequencing and bioinformatics analysis, the β-lactamase genes of 22 XDR/PDR-PA were listed in Table 1. "OXA-101 + OXA-847" was the most common type (9 isolates, 40.91%), followed by "OXA-50" (3 isolates, 13.64%), "OXA-846", "OXA-50 + OXA-573" (2 isolates, 9.09%) and "OXA-573 + OXA-846", "OXA-101 + OXA-573 + OXA-847", "OXA-847", "OXA-50", "OXA-488", "OXA-101, OXA-483, OXA-573" (1 isolate, 4.55%).

Antimicrobial susceptibility tests and synergy tests

MICs of CZA and amikacin alone or in combination against XDR/PDR-PA isolates were listed in Table 2. 2 isolates were susceptible to CZA, two isolates were intermediate to CZA, and the rest of the 18 isolates were resistant to CZA. After the combination of CZA and amikacin, MICs of both drugs against XDR/PDR-PA showed different degrees of reduction. According to the Loewe additivity index, the results of synergy tests of CZA in combination with amikacin suggested that 77.3% of the isolates showed synergistic effects, 9.1% showed additive effects, and only 13.6% showed indifferent effects.

Table 1 β-lactamase genes of 22 XDR/PDR *Pseudomonas aeruginosa* isolates

β-lactamases	*P. aeruginosa* isolate
OXA-101 + OXA-847	PA-3, PA-6, PA-7, PA-24, PA-28, PA-39, PA-46, PA-58, PA-86
OXA-573 + OXA-846	PA-11
OXA-50 + OXA-573	PA-22, PA-100
OXA-101 + OXA-573 + OXA-847	PA-47
OXA-847	PA-54
OXA-846	PA-67, PA-102
OXA-50	PA-71, PA-95, PA-97
OXA-101, OXA-483, OXA-573	PA-89
OXA-488	PA-98

PK/PD simulation

The probability of target attainment (PTA) and cumulative fraction of response (CFR) of CZA monotherapy or in combination with amikacin against XDR/PDR-PA infections was listed in Table 3. When PK/PD target was *50%f*T > MIC, CFR was 65.87% for CZA 2.5 g q8h monotherapy. CFR was 97.84% for CZA 2.5 g q8h when CZA in combination with amikacin. When PK/PD target was *50%f*T > 5*MIC, CFR was 8.98% for CZA 2.5 g q8h monotherapy. CFR was 31.41% for CZA 2.5 g q8h when CZA in combination with amikacin.

Table 4 shows the PTA and CFR of amikacin monotherapy or combined with CZA against XDR/PDR-PA infections. CFR was 27.93% and 34.46% for amikacin 25 mg/kg and 30 mg/kg monotherapy, respectively. Similarly, CFR was 41.25% and 43.37% for amikacin 25 mg/kg and 30 mg/kg monotherapy, respectively. As shown in Table 5 and Fig. 1, the MIC distributions of both CZA and amikacin were shifted to the left after the combination of CZA and amikacin.

Discussion

Pseudomonas aeruginosa has attracted increasing attention due to its acquired and robust natural resistance mechanisms. A key factor in this resistance is the production of β-lactamases, enzymes that hydrolyze β-lactam

Table 2 MICs of ceftazidime-avibactam and amikacin alone or in combination against XDR/PDR *Pseudomonas aeruginosa* isolates by FICI and Loewe additivity index analysis

P. aeruginosa isolate	CZA MIC (mg/L)			AMK MIC (mg/L)			Synergism analysis			
	CZA alone	CZA in combination	Fold reduction in CZA MIC	AMK alone	AMK in combination	Fold reduction in AMK MIC	FICI	S or I based on FICI	Loewe additivity index	S or A based on Loewe additivity index
PA-3	64	32	2	256	8	32	0.53	I	0.47	S
PA-6	64	8	8	128	64	2	0.63	I	0.37	S
PA-7	16	8	2	128	64	2	1	I	0	Additivity
PA-8	16	8	2	256	64	4	0.75	I	0.25	S
PA-11	32	8	4	4	2	2	0.75	I	0.25	S
PA-22	16	16	1	256	128	2	1.5	I	−0.5	Antagonistic
PA-24	64	32	2	64	16	4	0.75	I	0.25	S
PA-28	64	16	4	64	32	2	0.75	I	0.25	S
PA-39	64	0.5	128	128	64	2	0.51	I	0.49	S
PA-46	4	0.5	8	32	16	2	0.63	I	0.37	S
PA-47	32	8	4	16	4	4	0.5	S	0.5	S
PA-54	16	1	16	8	4	2	0.51	I	0.49	S
PA-58	32	16	2	128	32	4	0.75	I	0.25	S
PA-67	32	0.5	64	2	1	2	0.52	I	0.48	S
PA-71	64	16	4	8	2	4	0.5	S	0.5	S
PA-86	64	32	2	128	32	4	0.75	I	0.25	S
PA-89	4	4	1	256	128	2	1.5	I	−0.5	Antagonistic
PA-95	64	32	2	4	2	2	1	I	0	Additivity
PA-97	8	2	4	64	16	4	0.5	S	0.5	S
PA-98	32	8	4	2	1	2	0.75	I	0.25	S
PA-100	8	4	2	8	2	4	0.75	I	0.25	S
PA-102	16	8	2	4	4	1	1.5	I	−0.5	Antagonistic

CZA ceftazidime-avibactam, *AMK* amikacin, *FICI* fractional inhibitory concentration index, *S* synergy, *I* indifferent

Table 3 The probability target attainment (PTA) and cumulative fraction of response (CFR) of ceftazidime-avibactam monotherapy or in combination with amikacin against XDR/PDR-PA infections

PK/PD target	Dosing regimens	Treatment	PTA of different MICs								CFR (%)
			0.5	1	2	4	8	16	32	64	
*50%f*T > MIC	2.5 g q8h	Monotherapy	100	100	100	100	100	100	100	1.89	65.87
		Combination therapy	100	100	100	100	100	100	87.59	-	**97.84**
*50%f*T > 5*MIC	2.5 g q8h	Monotherapy	100	100	100	100	3.24	0	0	0	8.98
		Combination therapy	100	100	100	100	3.2	0	0	-	31.41

Table 4 The probability target attainment (PTA) and cumulative fraction of response (CFR) of amikacin monotherapy or in combination with ceftazidime-avibactam against XDR-PA infections

PK/PD target	Dosing regimens	Treatment	PTA of different MICs										CFR (%)
			0.5	1	2	4	8	16	32	64	128	256	
C_{max}/MIC > 8	25 mg/kg	Monotherapy	100	100	100	100	47.46	0	0	0	0	0	27.93
	30 mg/kg	Monotherapy	100	100	100	100	97.50	0	0	0	0	0	34.46
	25 mg/kg	Combination therapy	100	100	100	100	48.72	0	0	0	0	-	41.25
	30 mg/kg	Combination therapy	100	100	100	100	97.61	0	0	0	0	-	43.37

Table 5 MIC frequency of ceftazidime-avibactam (CZA) monotherapy or in combination with amikacin (AMK) against XDR-PA infections and amikacin (AMK) monotherapy or in combination with ceftazidime-avibactam (CZA) against XDR-PA infections

Treatment	MIC frequency (%)									
	0.5	1	2	4	8	16	32	64	128	256
CZA Monotherapy	-	-	-	9.09	9.09	22.73	22.73	36.36	-	-
CZA Combination therapy	13.64	4.54	4.54	9.09	31.82	18.18	18.18	-	-	-
AMK Monotherapy	-	-	9.09	13.64	13.64	4.54	4.54	13.64	22.73	18.18
AMK Combination therapy	-	9.09	18.18	13.64	4.55	13.64	13.64	18.18	9.09	-

antibiotics, rendering them ineffective. The most common β-lactamases in *P. aeruginosa* are AmpC enzymes [20]. These β-lactamases are typically chromosomally encoded and can be induced by exposure to specific antibiotics, such as cephalosporins. The presence of AmpC β-lactamases frequently results in resistance to a broad spectrum of β-lactam antibiotics, complicating treatment options.

Additionally, *P. aeruginosa* can acquire extended-spectrum β-lactamases (ESBLs) through horizontal gene transfer. These ESBLs, including TEM, SHV, and CTX-M types, confer resistance to newer β-lactams such as ceftazidime. The proliferation of ESBL-producing strains is an escalating concern in clinical settings due to their capacity to evade standard antibiotic therapies [21–23]. Another group of β-lactamases found in *P. aeruginosa* is the metallo-β-lactamases (MBLs). These enzymes, including VIM, IMP, and NDM types, are highly effective at hydrolyzing carbapenems, frequently used as a last resort for treating multidrug-resistant infections [24]. The prevalence of MBLs poses a significant threat to public health, as they confer resistance to nearly all β-lactam antibiotics. Currently, the most frequently reported β-lactamases in *P. aeruginosa* include class A enzymes (e.g., PER, VEB, GES, KPC), class B enzymes (e.g., NDM, VIM, IMP), and class D enzymes (e.g., OXA-2, OXA-10) [25].

In this study, the checkerboard method was utilized in vitro to evaluate the synergistic effect between CZA and amikacin. It was found that the combination of CZA and amikacin exhibited additive or synergistic effects in 86.4% (19/22) of these strains. ***Montero* et al**. applied time-kill experiments to explore the synergistic effect in vitro of 7 CZA-resistant XDR-PA isolates. It was found that the combination of CZA and amikacin showed additive or synergistic effects in 85% (6/7) of these strains [9]. The strain used in this study was XDR/PDR-PA, whereas ***Montero* et al.** conducted synergistic tests with XDR-PA. There is a difference in the proportion of strains exhibiting synergistic effects.

Additionally, whole genome sequencing technology and bioinformatics were applied to analyze the resistance genes

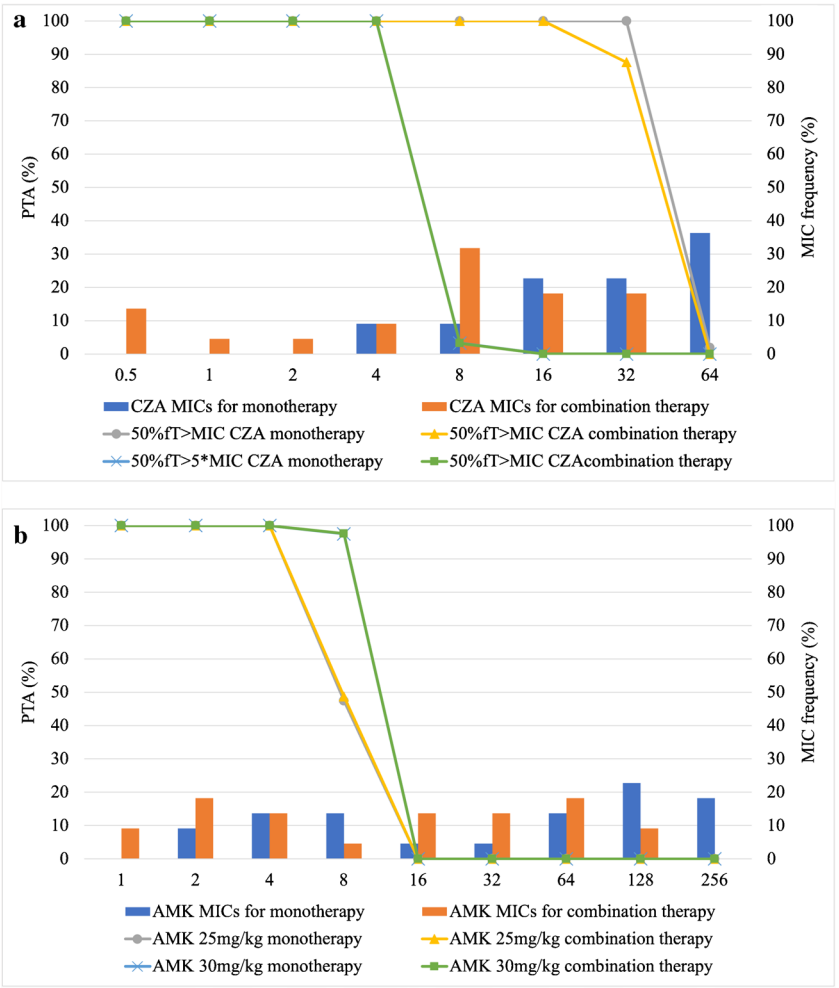

Fig. 1 **a**. MIC distributions of 22 *P. aeruginosa* clinical isolates (OXA-producing) in CZA MICs in monotherapy and combination therapy with amikacin and the probability of target attainment of an *f*T > MIC of 50% for CZA 2.5 g q8h dosing regimens. **b**. MIC distributions of 22 *P. aeruginosa* clinical isolates (OXA-producing) in AMK MICs in monotherapy and combination therapy with CZA and the probability of target attainment of a C_{max}/MIC > 8 for AMK 25 mg/kg or 30 mg/kg dosing regimens. PTA: probability of target attainment

of the strains. Based on the results of synergy experiments, it was found that CZA, in combination with amikacin, exhibited synergistic or additive effects in 88.89% of XDR/PDR-PA producing OXA-101 and OXA-847. Furthermore, in our team's previous study, it was found that XDR/PDR-PA, which produces OXA-101 and OXA-847, was widely spread in the First Medical Centre of the General Hospital of the People's Liberation Army, accounting for 32.84% (22/67) of the XDR/PDR-PA collected from sputum and respiratory specimens from January 2016 to November 2021 [18].

Therefore, CZA and amikacin can be combined to treat XDR/PDR-PA respiratory tract infections. This approach will help to maximize the likelihood of administering appropriate empirical anti-infective therapy to patients at the initial stage of the disease. Additionally, clinicians can adjust the anti-infective treatment regimen based on the results of drug susceptibility tests. However, this study is an in vitro experiment with a limited sample size. Extensive in vivo experiments and clinical trials with larger sample sizes are needed to verify the synergistic effect between the two drugs in the future.

Utilizing Monte Carlo simulations, the pharmacokinetic and pharmacodynamic parameters of both antimicrobial drugs were integrated to explore the pharmacodynamic attainment of the synergism of CZA in combination with amikacin against OXA-producing XDR/PDR-PA. Combining CZA with AMK can change the MIC distribution of both drugs to a greater extent, resulting in a large difference in CFR between monotherapy and combination therapy. Meanwhile, CZA, in combination with amikacin, can provide adequate PD exposure for OXA-producing XDR/PDR-PA infections. Additionally, it was found that the pharmacodynamic potentiation of amikacin was not significant when CZA was combined with amikacin to treat XDR/PDR-PA infections. Increased doses of amikacin did not provide adequate PD exposure. Amikacin, being an aminoglycoside, often causes various adverse effects. Therefore, amikacin can be used as an adjunct to enhance the efficacy of anti-infective therapy with CZA.

Our previous work demonstrated that optimized two-step-administration therapy (OTAT) could improve the PTA and CFR of CZA monotherapy for treating infections caused by

XDR/PDR-PA [18, 26]. To enhance the efficacy of the treatment of XDR/PDR-PA infections, the above two methods (i.e., CZA in combination with amikacin, OTAT of CZA monotherapy) could be attempted in clinical practice to increase the PD exposure of CZA. Clinicians can tailor different anti-infective treatment regimens based on the specific circumstances of the patient (e.g., general health condition, family financial situation, history of drug allergies, etc.).

This study investigated the in vitro synergistic effect and pharmacodynamic attainment of CZA combined with amikacin for treating XDR/PDR-PA using synergy tests and Monte Carlo simulations. Based on the results of this study, the pharmacodynamic attainment of the synergism of CZA in combination with amikacin for OXA-producing XDR/PDR-PA infection was considered. This provides an in vitro theoretical basis for the future combined application of CZA and amikacin in clinical anti-infection work.

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Author contributions Y. K. conducted all the experiments. The manuscript was written by Y. K. and revised by J.C.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval statement This work did not involve ethical issues. The study does not involve patients' privacy. No ethical approval was required.

Competing interests The authors declare no competing interests.

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