Efficacy of Cefiderocol against carbapenem-resistant *A. baumannii* and *P. aeruginosa* in ventilator-associated pneumonia mouse model

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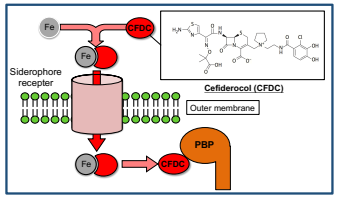
Introduction

Cefiderocol (CFDC) is a novel cephalosporin with siderophore structure, characterized by transportation through siderophore receptor on outer membrane of Gram-negative bacteria and structural stability against beta-lactamase. The antimicrobial activity against multidrug resistant bacteria is demonstrated *in vitro* and *in vivo*. In this study, we aimed to elucidate the *in vivo* efficacy of CFDC using ventilator-associated pneumonia (VAP) mouse model.



Methods

Antimicrobial susceptibility tests

The minimum inhibitory concentration (MIC) of CFDC and meropenem (MEPM) against the test *Acinetobacter baumannii* (Ab) and *Pseudomonas aeruginosa* (Pa) isolates were measured by broth microdilution assay. Iron depleted medium was used for CFDC.

VAP mouse model

For VAP mouse models, neutropenia was induced by cyclophosphamide intraperitoneal administration, followed by intubation of sterile tube in the trachea and inoculation of bacterial suspension.

PK analysis were performed in infected mice, in order to determine treatment regimens to achieve targeted time above MIC (TAM) of free concentrations in plasma. Treatment was initiated 3 hours post infection and continued up to 120 h for survival analysis. To investigate the bactericidal effect, the mice were sacrificed to count bacterial load in the lung at 48 h and 24 h for VAP-Ab and Pa, respectively.

Result

MICs of test isolates are shown in Table 1. Both isolates showed susceptibility against CFDC, but resistance against MEPM.

Table 1. MICs of antimicrobial agents against Ab and Pa

	CFDC	MEPM
Ab	0.5 (S)	128 (R)
Pa	0.008 (S)	16 (R)

MICs are shown as mg/L. Criteria from M100-S29 published by CLSI. S, susceptible; R, resistant.

Dosing regimen determined by PK analysis are shown in Table 2. These regimen is achievable in human for CFDC but not for MEPM.

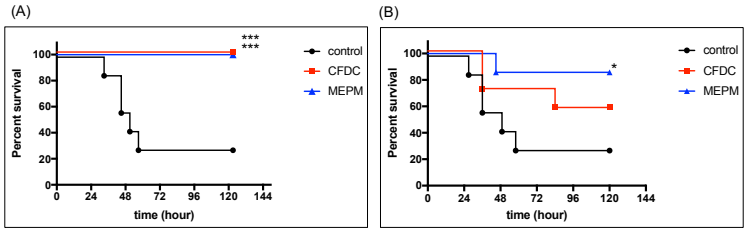
Table 2. Dosing regimen and fT>MIC against VAP model

VAP-Ab	dose	interval	f TAM
CFDC	55 mg/kg	6h	70.1 %
	210 mg/kg		90.5 %
	390 mg/kg		100 %
MEPM	1,100 mg/kg	6h	30.0 %

VAP-Pa	dose	interval	f TAM
CFDC	3 mg/kg	8h	76.0 %
	10 mg/kg		90.5 %
	30 mg/kg		100 %
MEPM	110 mg/kg	8h	30.0 %

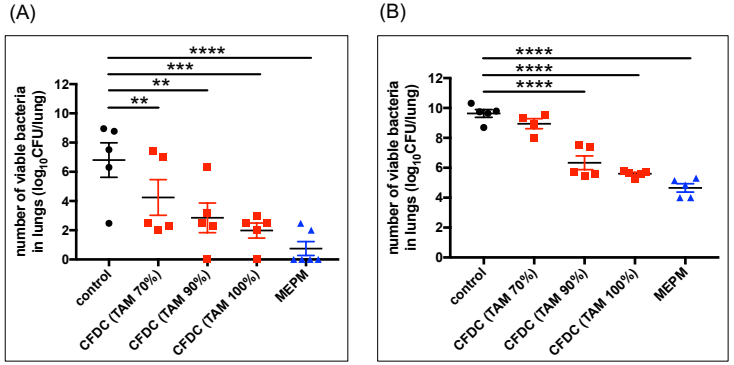
MEPM was administered with the same amount of cilastatin.

Survival study was conducted with CFDC (TAM 70%) and MEPM (TAM 30%). In VAP-Ab, survival improvement was observed in both CFDC and MEPM treated groups. In VAP-Pa, survival improvement was observed in MEPM but not in CFDC treated group.



The survival (Kaplan-Meier) curves of mice with VAP-Ab (A) and VAP-Pa (B) are shown (n=7, each group). At 3h post infection, the treatment with CFDC (TAM 70%) and MEPM combined with cilastatin (TAM 30%) were initiated. Log-rank (Mantel-Cox) test is performed. A *P* value < 0.008 is considered statistically significant. Seven mice per group were used. * *P* < 0.05; *** *P* < 0.001.

Bacterial load was compared between CFDC (TAM 70, 90, 100%) , MEPM (TAM 30%) and control. In treatment study for VAP-Ab (A), bactericidal effect was achieved at TAM > 70% in CFDC groups, as well as TAM 30% in MEPM group. In VAP-Pa (B), bactericidal effect was observed at TAM > 90% in CFDC groups, as well as TAM 30% in MEPM group.



Bacterial load in the lung of mice with VAP-Ab (A) and VAP-Pa (B) are shown. Dunnett's multiple comparisons test is performed. A *P* value < 0.05 is considered statistically significant. Five mice per group were used. ** *P* < 0.01, *** *P* < 0.001, **** *P* < 0.0001.

Conclusion

The efficacy of CFDC against VAP-Ab and Pa were demonstrated in this study. Although 90% free TAM was required for bactericidal effect, CFDC was shown to be effective against carbapenem-resistant Gram-negative pathogens at the recommended clinical dosing regimen.

This research was conducted in collaboration with SHIONOGI & Co., Ltd.