No. 1302

IDWeek 2020
21-25 October, 2020

Cefiderocol Population Pharmacokinetics and Probability of Target Attainment in Plasma and Epithelial Lining Fluid in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infections

Takayuki Katsube[1], Nao Kawaguchi[1], Roger Echols[2], Toshihiro Wajima[1], David P. Nicolau[3]

[1]Shionogi & Co., Ltd., Osaka, Japan; [2]Infectious Disease Drug Development Consulting, LLC, Easton, CT, USA; [3]Hartford Hospital, Hartford, CT, USA

Contact Information:
Takayuki Katsube
12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Kita-ku, Osaka 530-0012, Japan
Phone: +81-6-6485-5088 ; Fax: +81-6-6375-5780
E-mail: takayuki.katsube@shionogi.co.jp

Abstract

Background : Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a broad range of Gram-negative bacteria. The aim of this study was to perform population pharmacokinetic (PopPK) analysis and evaluate probability of target attainment (PTA) in plasma and epithelial lining fluid (ELF) based on a modeling and simulation approach.

Methods : PopPK analysis in plasma was conducted using 3427 concentration data from 425 patients with pneumonia, bloodstream infection/sepsis (BSI/sepsis), complicated urinary tract infection (cUTI), or acute uncomplicated pyelonephritis in 3 Phase 2 or 3 studies (NCT03032380, NCT02714595, and NCT02321800), and 91 subjects without any infection in Phase 1 studies. In addition, intrapulmonary modeling was conducted using ELF concentration data from 7 pneumonia patients (NCT03862040) and 20 healthy subjects. Monte-Carlo simulations were performed by generating 1000 virtual patients for each infection site (pneumonia, BSI/sepsis, or cUTI) to predict PTA for 75% of time for which free drug concentration in plasma or ELF (only pneumonia patients) exceeds the minimum inhibitory concentration (MIC; 0.25–16 μg/mL) over dosing interval following CFDC 2 g q8h infused over 3 hours with dose adjustment based on renal function, including augmented renal clearance.

Results : The developed PopPK model described the plasma and ELF CFDC concentrations. Creatinine clearance, body weight, infection site, and albumin concentration were statistically significant covariates on CFDC PK in plasma. There were no clinically significant differences in CFDC plasma exposure based on infection site or with/without ventilation. The penetration ratio of ELF to free plasma in pneumonia patients (0.340) was 1.3-fold higher than that in healthy subjects (0.263). As shown in the table below, plasma PTA was >90% against MICs ≤ 4 μg/mL, regardless of infection site and renal function. ELF PTA in pneumonia patients was >90% against MICs ≤ 2 μg/mL and >85% against MICs ≤ 4 μg/mL, regardless of renal function.

Conclusions : The recommended dosing regimen (2 g, q8h, 3-hr infusion) adjusted by renal function provided adequate exposure to CFDC in patients with infections caused by Gram-negative pathogens, irrespective of infection site and renal function.

Introduction

- Cefiderocol is a novel parenteral siderophore cephalosporin discovered by Shionogi & Co., Ltd., which exhibits antibacterial activity against various Gram-negative bacteria including carbapenem-resistant strains [1].
- Cefiderocol was approved in the USA for the treatment of complicated urinary tract infection (cUTI) including pyelonephritis and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by Gram-negative pathogens in adults [2] and also approved by European Medicines Agency for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options [3].
- Cefiderocol is mainly excreted unchanged via the kidneys and the clearance is dependent on renal function [4,5]. The pharmacokinetic/pharmacodynamic (PK/PD) index for cefiderocol is the percentage of time for which free drug concentration exceeds the minimum inhibitory concentration (MIC) over the dosing interval (% $fT_{>MIC}$). The mean % $fT_{>MIC}$ required for a 1-$\log_{10}$ reduction against Gram-negative pathogens was 54% to 88% for *Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia strains* in animal infection model [6].
- Patients provided blood samples through sparse sampling for PK analysis of cefiderocol in APEKS-NP [7], CREDIBLE-CR [8], and APEKS-cUTI [9]. Epithelial lining fluid (ELF) concentration data were obtained from 7 pneumonia patients. ELF concentrations at 2 hours after the end of infusion were higher than those at end of infusion, suggesting the delayed distribution of cefiderocol into ELF in pneumonia patients.
- The aim of this study was to build a population PK model based on the plasma concentration data from patients with nosocomial pneumonia, bloodstream infection/sepsis (BSI/sepsis), or cUTI, and subjects without any infection, and to build an intrapulmonary PK model based on plasma and ELF concentration data from pneumonia patients and healthy subjects. Probability of target attainment (PTA) for target % $fT_{>MIC}$ in plasma and ELF (% $fT_{>MIC,ELF}$) were calculated to assess the dosing regimens of cefiderocol.

Methods

1.1 Development of Population PK Model

- The population PK model was developed using 3427 cefiderocol plasma concentrations from 115 patients with pneumonia in the APEKS-NP study (NCT03032380), 72 patients with pneumonia, BSI/sepsis or cUTI in the CREDIBLE-CR study (NCT02714595), 238 patients with cUTI or acute uncomplicated pyelonephritis in the APEKS-cUTI study (NCT02321800) and 91 subjects without any infection in Phase 1 studies.
- A 3-compartment model was tested as a structural model.
- The following covariates were investigated; creatinine clearance calculated by Cockcroft–Gault equation (CrCL), body weight, age, albumin concentration (ALB), aspartate aminotransferase, alanine aminotransferase, total bilirubin, sex, race, infection site, and mechanical ventilation.
- The maximum concentration (C_{max}) and daily area under the concentration–time curve (AUC) for the patients were estimated using empirical Bayesian estimation of the final model.

1.2 Development of Intrapulmonary PK Model

- The intrapulmonary PK model was developed using 168 cefiderocol plasma concentrations and 27 ELF concentrations from 7 pneumonia patients (NCT03862040) and 20 healthy subjects in Phase 1 studies.
- An ELF compartment was incorporated into the above 3-compartment model for plasma data.
- The fraction of ELF to plasma concentration was estimated in pneumonia patients and healthy subjects, respectively. First-order rate constant between plasma and ELF compartments and inter-individual variability of the fraction were also estimated using individual post-hoc plasma PK parameters calculated by the population PK model.
- The penetration ratio of post-hoc AUC in ELF (AUC_{ELF}) to free plasma ($fAUC_{plasma}$) were calculated.

1.3 Monte-Carlo simulation

- Monte-Carlo simulations were performed to calculate PTA for 75% $fT_{>MIC}$, 100% $fT_{>MIC}$, 75% $fT_{>MIC,ELF}$, and 100% $fT_{>MIC,ELF}$. The % $fT_{>MIC}$ was calculated based on the simulated steady-state free plasma concentrations using unbound fraction of 0.422 [10]. For calculation of % $fT_{>MIC,ELF}$, total ELF concentrations were regarded as free ELF concentrations since the protein binding in ELF is expected to be low [11, 12]. The % $fT_{>MIC}$ and % $fT_{>MIC,ELF}$ were calculated against an MIC range of 0.25 to 16 μg/mL following 2 g infusion over 3 hours every 8 hours (q8h; standard dose of cefiderocol), with dose adjustment based on renal function.
- A thousand virtual patients with pneumonia, BSI/sepsis, or cUTI were generated by renal function group using the population PK model and intrapulmonary PK model. PTA was calculated by infection site and renal function group. The PTA integrated with all renal function groups was also calculated by weighting proportions of patients in each renal function group based on the distribution of CrCL in Phase 3 studies.

1.4 Software

- Model building and Monte-Carlo simulation were performed using NONMEM (version 7.3) [13], Perl-speaks NONMEM (version 4.2.0) [14], and Pirana (version 2.9.4). R (version 3.5.1) [15] was used to calculate PTA.

Result

- The background characteristics of the patient population used for the population PK modeling and intrapulmonary PK modeling are shown in **Table 1**.
- The parameter estimates for the final population PK model and intrapulmonary PK model are provided in **Table 2**.
- CrCL, body weight, infection site, and ALB were significant covariates on cefiderocol PK. The most influential covariate was CrCL, as expected. The CL in patients with pneumonia, BSI/sepsis, or cUTI was suggested to be comparable to that in subjects without infection. Volume of distribution in patients with infection was suggested to be 39% higher than that in subjects without infection.
- Post-hoc estimates of C_{max} and daily AUC in plasma overlapped among infection sites and between patients with and without mechanical ventilation (**Figure 1**). The geometric means (range) of estimated free trough concentrations were 16.3 (2.91 to 84.8) μg/mL in the CREDIBLE-CR study and 12.7 (0.856 to 89.5) μg/mL in the APEKSNP study.
- In the intrapulmonary PK modeling, the fraction of ELF to total plasma concentration in pneumonia patients was estimated to be 1.4-fold higher than that in healthy subjects. The penetration ratios of AUC_{ELF} to $fAUC_{plasma}$ were 0.340 in pneumonia patients and 0.263 in healthy subjects. The median of simulated ELF trough concentrations at steady state was higher than 4 μg/mL in all renal function groups.
- Plasma PTA for 75% $fT_{>MIC}$ was > 90% against MICs ≤ 4 μg/mL in any infection site and renal function group. The PTA even for 100% $fT_{>MIC}$ was > 90% against MICs ≤ 4 μg/mL for all of the infection sites and renal function groups except for the normal renal function in BSI/sepsis patients (85%). ELF PTA for 75% $fT_{>MIC,ELF}$ was > 90% against MICs ≤ 2 μg/mL and >85% against MICs ≤4 μg/mL in any infection site and renal function group. Even the PTA for 100% $fT_{>MIC,ELF}$ was > 85% against MICs ≤ 4 μg/mL regardless of renal function (**Table 3**).
- PTA integrated with all renal function groups for both 100% $fT_{>MIC}$ and 100% $fT_{>MIC,ELF}$ were >90% against MICs ≤ 4 μ g/mL in any infection site (**Figure 2**).

Table 1. Background Characteristics in the Analysis Population for Population PK Model and Intrapulmonary PK Model

	Population PK model				Intrapulmonary PK model	
					Phase 1 studies	
	Phase 1 studies (N = 91)	Phase 2 APEKS-cUTI study (N = 238)	Phase 3 APEKS-NP study (N = 115)	Phase 3 CREDIBLE-CR study (N = 72)	Healthy subjects (N = 20)	Pneumonia patients (N = 7)
Age (years)	36.0 (20 - 74)	65.0 (18 - 93)	68.0 (18 - 91)	67.5 (21 - 92)	25.0 (21 - 36)	70.0 (19 - 78)
Body weight (kg)	68.4 (45.1 - 124.1)	76.4 (46.3 - 138.0)	72.0 (28.9 - 130.0)	68.4 (25.0 - 156.0)	61.9 (54.9 - 72.3)	88.1 (69.4 - 113.0)
CrCL (mL/min)	121.0 (7 - 185)	83.0 (25 - 186)	69.0 (5 - 306)	73.0 (10 - 540)	125 (95 - 148)	78 (44 - 275)
Albumin (g/dL)	4.2 (3.1 - 4.8)	4.2 (2.5 - 5.3)	3.0 (1.2 - 4.5)[a]	2.7 (1.6 - 4.8)[c]	4.7 (4.3 - 4.9)	2.8 (1.5 - 3.0)
Aspartate aminotransferase (U/L)	18.0 (10 - 45)	18.0 (6 - 101)	27.6 (3 - 139)[b]	36.0 (10 - 367)[d]	17 (11 - 28)	41 (22 - 259)
Alanine aminotransferase (U/L)	18.0 (5 - 51)	15.0 (4 - 111)	26.4 (4 - 116)[b]	26.5 (6 - 153)	18 (8 - 38)	29 (13 - 123)
Total bilirubin (mg/dL)	0.78 (0.20 - 2.00)	0.53 (0.19 - 2.88)	0.64 (0.10 - 2.26)[c]	0.56 (0.15 - 15.20)[d]	0.8 (0.5 - 1.5)	0.7 (0.3 - 3.9)
Sex (male : female) [#]	75 (82.4%) : 16 (17.6%)	108 (45.4%) : 130 (54.6%)	78 (67.8%) : 37 (32.2%)	48 (66.7%) : 24 (33.3%)	20 (100%) : 0 (0%)	3 (42.9%) : 4 (57.1%)
Race (Asian : White : Black : Native : the others) [#]	49 (53.9%): 23 (25.3%): 17 (18.7%) : 1 (1.1%) :1 (1.1%)	7 (2.9%): 230 (96.6%): 0 (0.0%) : 0 (0.0%) :1 (0.4%)	36 (31.3%): 78 (67.8%): 0 (0.0%) : 0 (0.0%) :1 (0.9%)	22 (30.6%): 42 (58.3%): 0 (0.0%) : 0 (0.0%) :8 (11.1%)	20 (100%) : 0 (0%) : 0 (0%) : 0 (0%) : 0 (0%)	0 (0%) : 5 (71.4%) : 1 (14.3%) : 0 (0%) : 1 (14.3%)
Infection site (pneumonia: BSI/sepsis : cUTI : no infection)	0 (0.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	0 (0.0%) : 0 (0.0%) : 238 (100.0%) : 0 (0.0%)	115 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	31 (43.1%) : 20 (27.8%) : 21 (29.2%) : 0 (0.0%)	0 (0.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	7 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)

Median (range). CrCL = creatinine clearance calculated by Cockcroft-Gault equation; Black = Black or African American; Native = native American or Alaska native.
[#] Number of subjects (percentage of all subjects). [a] N = 112. [b] N = 113. [c] N = 71. [d] N = 69. [e] N = 68.

Table 2. Parameter Estimates for Population PK Model and Intrapulmonary PK Model

	Pharmacokinetic parameters	Units	Estimates	%RSE
Population PK Model[a]	CL	(L/hr)	4.04	1.8
	V1	(L)	7.78	5.2
	Q2	(L/hr)	6.19	5.7
	V2	(L)	5.77	3.2
	Q3	(L/hr)	0.127	14.1
	V3	(L)	0.798	6.4
	Effect of CrCL on CL (CrCL cut-off value:150 mL/min)		0.682	4.0
	Effect of body weight on V1 and V2		0.580	12.2
	Effect of infection with pneumonia on CL		0.981	4.1
	Effect of infection with BSI/sepsis on CL		1.08	10.4
	Effect of infection with cUTI on CL		0.872	6.4
	Effect of albumin concentration on V1		-0.617	10.9
	Effect of infection on V1		1.39	6.7
Intrapulmonary PK Model	Inter-individual variability (CV %) [η_{CL}]			
	CL	%	37.5 (3.6)	10.4
	V1	%	56.9 (13.6)	19.8
	V2	%	33.6 (18.2)	35.0
	Covariance between CL and V1		0.0886 (R = 0.415)	29.1
	Covariance between CL and V2		0.0792 (R = 0.629)	33.2
	Covariance between V1 and V2		0.150 (R = 0.784)	27.3
	Intra-individual variability (CV %) [ε_{CL}]			
	Proportional residual error	%	20.5 (13.2)	5.1
	FRC in healthy subjects		0.103	6.2
	Effect of pneumonia patients on FRC		1.39	19.6
	First-order rate constant between plasma and ELF concentrat (hr^{-1})		0.151	63.4
	Inter-individual variability (CV %) [η_{FRC}]			
	FRC	%	34.6	34.9

CL = total clearance; V1, V2, V3 = volume of distribution in the central and peripheral compartments; Q2 and Q3 = intercompartmental clearance; CV = coefficient of variation; η, ε, ξ = shrinkage in the standard deviation of inter-individual variability parameters η, ε, ξ = shrinkage in the standard deviation of intra-individual variability parameters ε; %RSE = relative standard error in percent; R = coefficient of correlation; FRC = fraction of ELF to total plasma concentration.

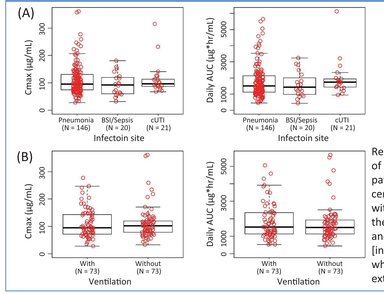
[a] CrCL ≤ 150 mL/min; CL = 4.04 * (CrCL/83.0) $^{-0.682}$ * (0.981 for patients with pneumonia) * (1.08 for patients with BSI/sepsis) * (0.872 for patients with cUTI)

CrCL ≥ 150mL/min; CL = 4.04 * (150/83.0) $^{-0.682}$ * (0.981 for patients with pneumonia) * (1.08 for patients with BSI/sepsis) * (0.872 for patients with cUTI)

V1 = 7.78 * (body weight/72.6) $^{0.580}$ * (albumin/3.9) $^{-0.617}$ * (1.39 for patients with infection)

V2 = 5.77 * (body weight/72.6) $^{0.580}$

Figure 1. Box Plot for Post-hoc Plasma C_{max} and Daily AUC by Infection Site (A) and by Ventilation Status in Pneumonia Patients (B)



Red circle: post-hoc estimates of parameters for individual patients. Horizontal black center line represents median, with the top and the base of the boxes representing first and third quartiles (interquartile range (IQR)], whiskers represent the most extreme data within 1.5 × IQR.

Figure 2. PTA Integrated with All Renal Function Groups for 100% $fT_{>MIC}$ and 100% $fT_{>MIC,ELF}$

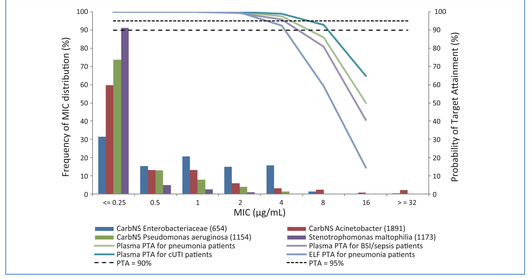


Table 3. PTA for 100% $fT_{>MIC}$ and 100% $fT_{>MIC,ELF}$ by Infection Site and Renal Function Group

Target	Renal function group	Dose regimens with 3-hr infusion	Probability of target attainment for 100% $fT_{>MIC}$ or 100% $fT_{>MIC,ELF}$ MIC (μg/mL) 0.25	0.5	1	2	4	8	16
Pneumonia patients									
100% $fT_{>MIC}$ (Plasma)	Augmented renal function	2 g q6h	100	100	100	99.7	95.9	79.8	37.0
	Normal renal function	2 g q8h	100	100	99.9	98.3	91.2	64.6	23.2
	Mild renal impairment	2 g q8h	100	100	99.9	99.7	98.2	85.9	46.4
	Moderate renal impairment	1.5 g q8h	100	100	100	100	99.5	94.8	66.7
	Severe renal impairment	1 g q8h	100	100	100	100	100	99.5	81.8
	ESRD	0.75 g q12h	100	100	100	100	100	98.3	77.1
100% $fT_{>MIC,ELF}$ (ELF)	Augmented renal function	2 g q6h	100	100	100	99.8	91.8	53.9	10.7
	Normal renal function	2 g q8h	100	100	100	99.5	87.0	41.8	6.0
	Mild renal impairment	2 g q8h	100	100	100	99.7	93.1	58.8	14.4
	Moderate renal impairment	1.5 g q8h	100	100	100	100	95.8	65.6	17.5
	Severe renal impairment	1 g q8h	100	100	100	99.9	97.7	74.5	24.7
	ESRD	0.75 g q12h	100	100	100	99.9	99.8	81.9	40.1
BSI/sepsis patients									
100% $fT_{>MIC}$ (Plasma)	Augmented renal function	2 g q6h	100	100	100	99.4	93.6	71.6	28.5
	Normal renal function	2 g q8h	100	99.9	99.5	96.2	85.8	54.0	14.1
	Mild renal impairment	2 g q8h	100	100	99.8	99.4	96.0	78.0	36.1
	Moderate renal impairment	1.5 g q8h	100	100	100	99.9	98.7	91.2	55.8
	Severe renal impairment	1 g q8h	100	100	100	100	100	98.3	74.7
	ESRD	0.75 g q12h	100	100	100	100	100	96.8	68.0
cUTI patients									
100% $fT_{>MIC}$ (Plasma)	Augmented renal function	2 g q6h	100	100	100	100	98.0	88.3	51.1
	Normal renal function	2 g q8h	100	100	99.9	99.4	95.1	77.6	34.3
	Mild renal impairment	2 g q8h	100	100	100	99.8	98.9	93.2	59.4
	Moderate renal impairment	1.5 g q8h	100	100	100	100	99.8	97.7	79.1
	Severe renal impairment	1 g q8h	100	100	100	100	100	99.7	90.1
	ESRD	0.75 g q12h	100	100	100	100	100	99.4	85.7

The shaded are indicates > 90%.

Conclusion

- The recommended dosing regimen of 2 g infused over 3 hours q8h, and the doses adjusted based on renal function, provided adequate exposure to cefiderocol in patients with infections caused by carbapenem-resistant Gram-negative pathogens, regardless of infection site and renal function, achieving high % $fT_{>MIC}$ in plasma and ELF up to an MIC of 4 μg/mL with high probability.

References

1. Yamano Y. Clin Infect Dis 2019;69(Suppl 7):S544–S551.
2. Fetroja® (cefiderocol) injection for intravenous use. Prescribing Information. Shionogi Inc., Florham Park, NJ, USA; 2020.
3. European Medicines Agency. Fetcroja (cefiderocol). Summary of opinion (initial authorisation). Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion. Accessed: 28 February 2020.
4. Katsube T, et al. J Clin Pharmacol 2017;57(5):584–591.
5. Katsube T, et al. 2017;61(1):e01381-16.
6. Nakamura R, et al. Antimicrob Agents Chemother 2019;63 (9):pii:e02031-18.
7. Wunderink RG, et al. Lancet Infect Dis 2020. Accepted.
8. Bassetti M, et al. Lancet Infect Dis 2020. Accepted.
9. Portsmouth S, et al. Lancet Infect Dis 2018;18(12):1319–1328.
10. Katsube T, et al. J Antimicrob Chemother 2019;74(7):1971–1974.
11. Craig WA, et al. Antibiotics in Laboratory Medicine 1986; 477-513.
12. Kiem S, et al. Antimicrob Agents Chemother 2008; 52: 24-36.
13. Beal SL, Sheiner LB, Boeckmann AJ, eds. NONMEM users guide (1989–2008). Icon Development Solutions, Ellicott City, MD. 1989–2006.
14. Lindbom L, et al. Comput Methods Programs Biomed 2005;79:241–257.
15. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.

QR code URL: https://shionogi.pub/IDWeek2020/Cefiderocol_poster1302-PKELF.pdf