Pharmacodynamics (PD) of the Beta-Lactamase Inhibitor Xeruborbactam When Administered in Combination with Meropenem

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Introduction

- Resistance to β-lactam antibiotics due to the increasing variety of β-lactamase enzymes has become a major clinical issue.
- Xeruborbactam (XERU) is a member of a new class of cyclic boronic acid β-lactamase inhibitors with inhibitory activity against major members of Class A, B, C, and D beta-lactamases.
- The combination is highly active in vitro against gram-negative pathogens including carbapenem resistant Enterobacterales (CRE), carbapenem-resistant *A. baumannii* (CRAB) and *P. aeruginosa*.
- The purpose of these studies was to determine the XERU pharmacokinetic and PK-PD measures that best described the activity of a fixed dosage regiment of meropenem against KPC or OXA beta-lactamase producing, carbapenem-resistant *Klebsiella pneumoniae* and *A. baumannii* in the neutropenic mouse thigh infection model.

Methods

Mouse Pharmacokinetics

- Neutropenic, infected, female Swiss-Webster mice were administered single doses ranging from 10 to 100 mg/kg by the intraperitoneal route. Additional studies assessed drug accumulation using doses of 12.5 and 30 mg/kg administered every 2 hours for 12 total doses.
- Blood samples (N = 3/timepoint) were collected at various timepoints over 24 hours.
- Plasma levels were determined using an LC-MS/MS method and the data were fit to a non-compartmental model (WinNonlin).

Mouse Thigh Infection Model

- Female Swiss-Webster mice were used.
- Mice were rendered temporarily neutropenic by the administration of 150 mg/kg of cyclophosphamide (Baxter, IL) on days −4 and −1 prior to infection.
- Infection was initiated (under isoflurane anesthesia) *via* an intramuscular injection of 0.1 mL of inoculum (~ 10^6 CFU/thigh).
- Treatment was initiated 2 h post-infection
- Controls were euthanized at the start of treatment while treated animals were euthanized 24 hours post-treatment using CO_2; thighs were removed aseptically, homogenized in 5 mL of saline, and plated on Mueller-Hinton Agar.

Pharmacodynamic Modeling

- The relationship between the PD measures and the change in log CFU compared to the start of treatment were fitted using the following inhibitory effect (Emax) model (Phoenix 64; Certara, Princeton, NJ):

$$Emax = E0 - (Imax \times X\gamma)/(X\gamma + IC50\gamma)$$

where E0 is the effect when X is equal to 0 (i.e., for the untreated control animals), Imax is the maximum reduction in the log number of CFU/lung, X is the PD measure, IC50 is the PD parameter (X) corresponding to 50% of the maximum bacterial reduction, and γ is the steepness of the curve.

Results

Figure 1. Xeruborbactam Pharmacokinetic and PK-PD Measures Associated with Activity in Combination with Meropenem Equivalent of 2g every 8 hours by 3-hour infusion in Humans against Seven Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) Isolates in the Neutropenic Mouse Thigh Infection Model

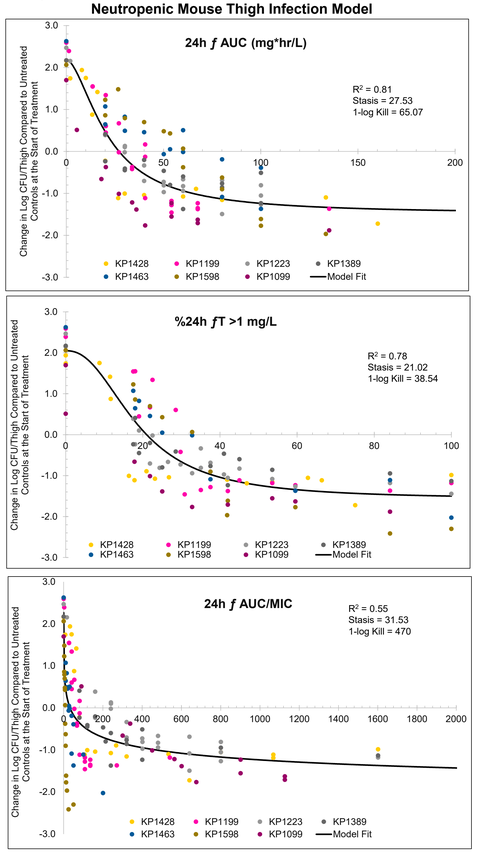

Figure 2. Xeruborbactam Pharmacokinetic and PK-PD Measures Associated with Activity in Combination with Meropenem Equivalent of 2g every 8 hours by 3-hour infusion in humans against Six ~~Different~~ Carbapenem-Resistant *A. baumannii* (CRAB) Isolates in the Neutropenic Mouse Thigh Infection Model

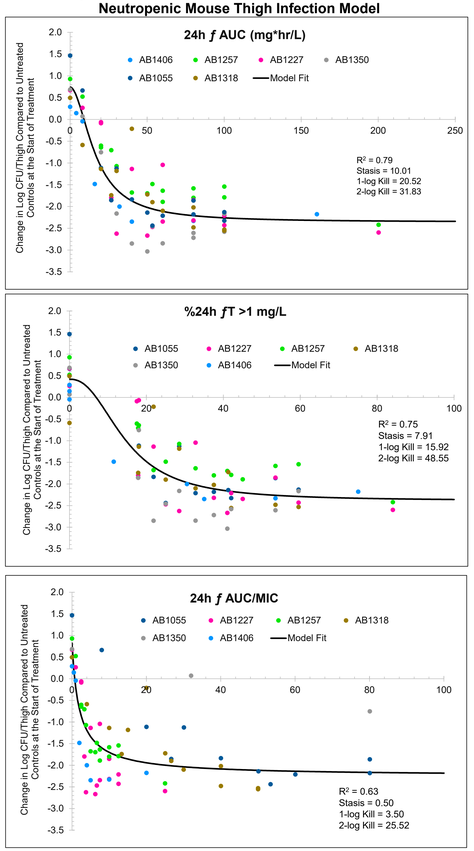

Table 1. Susceptibility Profile of Strains Used in In Vivo Studies

Strains	β-lactamases Present	Other Resistance Mechanisms (porins, efflux, etc.)	Meropenem MIC (mg/L)	
			Alone	w/ 8mg/L Xeru
A. baumannii AB1055	OXA-23	Not Determined	> 64	1
A. baumannii AB1227	OXA-23	Not Determined	64	8
A. baumannii AB1257	OXA-23,TEM-1D	Not Determined	64	8
A. baumannii AB1318	OXA-72	Not Determined	> 64	2
A. baumannii AB1406	OXA-23,TEM-1D	Not Determined	> 64	8
A. baumannii AB1350	OXA-24	Not Determined	> 64	0.25
K. pneumoniae KP1099	KPC-2, SHV-11, SHV12, CTX-M-14	OmpK35/OmpK36 (FS aa#29/GD)	> 64	≤0.06
K. pneumoniae KP1199	KPC-3, TEM, SHV	OmpK35/OmpK36 (FS aa#42/IS nt#246)	> 64	0.5
K. pneumoniae KP1223	KPC-2, SHV, TEM	OmpK35/OmpK36 (FS aa#29/GD)	> 64	0.125
K. pneumoniae KP1389	KPC-2, TEM, SHV	OmpK35/OmpK36 (FS aa#42/GD)	> 64	0.25
K. pneumoniae KP1428	TEM, SHV, CTX-M-15, OXA-48	OmpK35/OmpK36 (FS aa#255/IS nt#120)	64	0.125
K. pneumoniae KP1463	KPC, TEM, SHV, CTX-M-14	OmpK35/OmpK36 (FS aa#29/TGA aa#94)	> 64	2
K. pneumoniae KP1598	KPC-2 SHV CTX-M-14	OmpK35/OmpK36 (FS aa#29/GD)	> 64	8

Table 2. Single Dose Pharmacokinetics of Meropenem and Xeruborbactam in Mice

Compound	Dose (mg/kg)	AUC $_{0-\infty}$ (mg*hr/L)	CL/F (L/hr/kg)	Cmax (mg/L)	$T_{1/2}$ (h)
Meropenem	300	145.79	2.06	326.81	0.19
QPX7728	10	28.52	0.35	39.20	1.55
QPX7728	30	70.01	0.43	95.30	1.43
QPX7728	100	223.08	0.45	337.00	1.27

Table 3. Meropenem 24h Free Plasma AUC and %24h ƒT>MIC in Mice and Humans.

Species	Dosage Regimen	%24h ƒT>MIC at MIC mg/L										24h Free AUC mg*h/L
		128	64	32	16	8	4	2	1	0.5	0.25	
Human	2000 mg TID by 3-hour infusion	0	0	18.8	44.4	60.0	75.1	87.1	100	100	100	392
Mouse	300 mg/kg q2h	20	30	41.5	51	60.5	70	79	89	100	100	1575

Table 4. Xeruborbactam Pharmacokinetic and PK-PD Measures

Organism	24h ƒ XERU AUC			%24h ƒ XERU > 1			%24h ƒ XERU > 2			%24h ƒ XERU > 4			24h ƒ XERU AUC/MIC		
	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill
A. baumannii (6 strains)	0.79	10	20.5	0.75	7.9	15.9	0.69	1.7	7.9	0.38	0	1.5	0.63	0.5	3.5
Enterobacterales (7 strains)	0.81	27.5	65.1	0.78	21	38.5	0.69	13	30.4	0.58	7.1	17.2	0.55	31.5	470

Summary

- XERU reduced meropenem MICs to ≤ 8 mg/L in KPC and OXA producing carbapenem-resistant KP and carbapenem-resistant *A. baumannii* isolates. Of note, several of the KP strains also had intrinsic resistance mechanisms along with beta-lactamase production (Table 1).
- The pharmacokinetic profile of XERU is roughly, proportional to dose up to 100 mg/kg (Table 2). When dosing at 12.5 or 30 mg/kg every 2 hours for 12 doses, there was minimal accumulation at either dose level (data not shown).
- The XERU PK and PK-PD measures that best described the bacterial killing with a fixed dosage regimen of meropenem in combination with XERU against both KP and CRAB are 24h ƒ XERU AUC and %24h ƒ XERU > 1 mg/L. (Table 3; Figures 1 and 2).
- The magnitude of the XERU PK and PK-PD measures that best describe the activity of xeruborbactam against KP were 27.5 mg-h/L for stasis and 65.1 mg-h/L for 1-log of bacterial killing for 24h ƒ XERU AUC. For %24h ƒ XERU > 1 mg/L, it was 21% for stasis and 38.5% for 1-log of bacterial killing (Table 4).
- The magnitude of the XERU PK and PK-PD measures that best describe the activity of xeruborbactam against CRAB were 10 mg-h/L for stasis and 20.5 mg-h/L for 1-log of bacterial killing using 24h ƒ XERU AUC, and 7.9% for stasis and 15.9% for 1-log of bacterial killing for %24h ƒ XERU > 1 mg/L (Table 4).
- Based on the microbiological surveillance, Phase 1 clinical data (IDWeek 2022, Abstract 216), and these PK-PD indices, a xeruborbactam dosage regimen of 750 mg/day in combination with meropenem in humans would provide at least 1-log of bacterial killing for > 90% of isolates of serine carbapenemase-producing CRE and CRAB.
- Continued development of xeruborbactam in combination with meropenem for the treatment of serious infections due to carbapenem-resistant pathogens is warranted.

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