In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) Against 511 Gram-negative Clinical Isolates Obtained From Cancer Patients

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ABSTRACT

Background:
Patients with cancer develop bacterial infections often, especially during periods of neutropenia. Increasing problems with older agents (reduced susceptibility, overt resistance, and toxicity) has highlighted the need to develop newer agents. Ceftazidime-avibactam is a novel agent and is bactericidal against β-lactamase-producing
Gram-negative bacilli that might be useful in this setting.

Methods:
Clinical bacterial isolates were collected from the patient with blood stream infection at University of Texas MD Anderson Cancer Center. The minimum inhibitory concentration (MIC) of 511 gram negative isolates were determined for different antibiotics CAZ-AVI, meropenem (MEM), ceftazidime (CAZ), piperacillin-tazobactam (TZP)
and cefepime (FEP) using the broth microdilution method in accordance with CLSI guidelines. All samples were tested in duplicate. Isolates were stratified by species and resistance profile, including extended spectrum B-lactamase (ESBL +, ESBL -) and carbapenemase production. . MIC50 and MIC90analyses were conducted to examine antibiotic resistance.

Results:
CAZ-AVI was active against (ESBL- , ESBL+ Phenotype Escherichia coli and K. pneumoniae including ESBL+strains. MIC50/MIC90 of 0.6/1 ug/ml; Among non MDR P. aeruginosa strains the MIC50/MIC90 were 2/4 ug/ml ; for MDR P. aeruginosa strains the MIC50/MIC90 were 4/>32 ug/ml ,However the MIC90 for MEM, CAZ, TZP and FEP were >32, 64,256 and 64 respectively. Ceftazidime-avibactam was highly active against carbapenem resistant Enterobacteriaciae (CRE) MIC50/MIC90, 1/4 ug/ml. Compared to CAZ, TZP, and FEP.

Conclusion:
CAZ-AVI demonstrated potent activity against a large collection of gram-negative organisms identified in our cancer patients. CAZ-AVI was more active than currently available B- lactams, including against organisms that are resistant to most currently available agents, such as CRE and MDR P. aeruginosa strains.

INTRODUCTION

- Increasing problems with older agents (reduced susceptibility, overt resistance, and toxicity) has highlighted the need to develop newer agents that might be useful in this setting.
- Ceftazidime-avibactam is a novel agent and it is bactericidal against β-lactamase-producing Gram-negative bacilli that are not inhibited by ceftazidime alone. Avibactam serves to broaden the spectrum of ceftazidime versus ß-lactamase-producing Gram-negative bacilli.
- Clinical trials to date have reported that ceftazidime-avibactam is as effective as standard carbapenem therapy in complicated intra-abdominal infection and complicated urinary tract infection, including infection caused by cephalosporin-resistant Gram-negative isolates.
- Potential future roles for ceftazidime-avibactam include the treatment of suspected or documented infections caused by resistant Gram-negative-bacilli producing extended-spectrum ß-lactamase (ESBL), Klebsiella pneumoniae carbapenemases (KPCs) and/or AmpC ß-lactamases.

MATERIALS AND METHODS

- Organisms were obtained for testing only after approval of this study by the Institutional Review Board (IRB). Only one isolate per patient was tested in order to avoid testing clones of the same strain. The majority (>90%) of the isolates tested were from blood culture specimens with the remaining isolates cultured from lower respiratory infections.
- The mean inhibitory concentration (MIC) of 500 gram negative positive isolates were tested for 6 different antibiotics using micro broth dilution according to CLSI standard microbroth dilution methods. .
- Isolates were stratified by species and resistance profile (ESBL +, ESBL -, CRE) and MIC50 and MIC90 analyses were conducted to examine antibiotic resistance.

RESULTS

Table 1

	Antimicrobial Agent	MIC50 (ug ml^{-1})	MIC90 (ug ml^{-1})	Range
E. coli (ESBL-)	Mero	0.015	0.06	0.008-4
n=100	Taz	0.25	32	0.06 to >64
	SXT	>32/608	>32/608	0.06/1.2 to >32/608
	TGC	0.5	1	0.25-8
	P/T4	4/4	128/4	1/4 to >256/4
	FEP	0.06	4	0.015 to >64
	CZA	0.06/4	0.25/4	0.015/4-8/4
E. coli (ESBL+)	Mero	0.015	1	0.008-8
n=50	Taz	8	>64	0.12 to >64
	SXT	0.12/2.4	>32/608	0.06/1.2 to >32/608
	TGC	0.25	1	0.25-1
	P/T4	4/4	>256/4	2/4 to >256/4
	FEP	8	>64	0.03 to >64
	CZA	0.06/4	1/4	0.015/4-16/4
K. pneumo (ESBL-)	Mero	0.015	4	0.015 to >32
n=30	Taz	0.12	4	0.03 to >64
	SXT	0.25/4.8	>32/608	0.06/1.2 to >32/608
	TGC	1	4	0.5-8
	P/T4	4/4	>256/4	0.5/4 to >256/4
	FEP	0.06	>64	0.008 to >64
	CZA	0.06/4	1/4	0.015/4-16/4
K. pneumo (ESBL+)	Mero	0.03	1	0.012-2
n=27	Taz	>64	>64	0.5 to >64
	SXT	>32/608	>32/608	0.12/2.4 to >32/608
	TGC	2	8	0.5-8
	P/T4	32/4	>256/4	2/4 to >256/4
	FEP	64	>64	0.25 to >64
	CZA	0.24/4	1/4	0.03/4-4/4
K. pneumo (CRE)	Mero	32	>32	0.03 to >32
n=28	Taz	>64	>64	32 to >64
	SXT	>32/608	>32/608	0.12/2.4 to >32/608
	TGC	4	8	0.5 to 8
	P/T4	>256/4	>256/4	64/4 to >256/4
	FEP	>64	>64	8 to >64
	CZA	1/4	16/4	0.06/4 to >32/4

RESULTS (CONT'D)

Table 2

	Antimicrobial Agent	MIC50 (ug ml^{-1})	MIC90 (ug ml^{-1})	Range
Eb cloacae	Mero	0.03	0.12	0.015 to >32
n=34	Taz	0.25	>64	0.12 to >64
	SXT	0.25/4.8	>32/608	0.06/1.2 to >32/608
	TGC	1	4	0.25-8
	P/T4	4/4	128/4	1/4 to >256/4
	FEP	0.06	2	0.015 to >64
	CZA	0.25/4	1/4	0.03/4 to >32/4
Serratia	**Mero**	**0.25**	**0.5**	**0.025-1**
n=30	Taz	0.5	1	0.12-32
	SXT	0.5/9.5	8/152	0.12/2.4 to >32/608
	TGC	2	4	1-8
	P/T4	4/4	8/4	1/4 to >256/4
	FEP	0.5	2	0.06-8
	CZA	0.5/4	1/4	0.12/4-1/4
P. aeruginosa (Sens)	Mero	0.5	2	0.03 to >32
n=70	Taz	2	32	0.5 to >64
	SXT	16/304	32/608	2/38 to >32/608
	TGC	8	16	2 to >32
	P/T4	4/4	64/4	0.25/4 to >256/4
	FEP	2	16	0.25-64
	CZA	2/4	4/4	0.5/4 to >32/4
P. aeruginosa (MDR)	Mero	8	>32	0.12 to >32
n=51	Taz	8	64	1 to >64
	SXT	>32/608	>32/608	2/38 to >32/608
	TGC	16	>32	4 to >32
	P/T4	64/4	>256/4	4/4 to >256/4
	FEP	16	64	1 to >64
	CZA	4/4	>32/4	1/4 to >32/4
S. maltophilia	Mero	>32	>32	1 to >32
n=41	Taz	64	>64	1 to >64
	SXT	>32/608	>32/608	0.06/1.2 to >32/608
	TGC	4	8	0.1-16
	P/T4	>256/4	>256/4	16/4 to>256/4
	FEP	64	>64	2 to >64
	CZA	32/4	>32/4	0.5/4 to >32/4

CONCLUSIONS

- ✓ Ceftazidime – Avibactam demonstrated potent activity against a large collection of Gram-negative organisms identified in our cancer patients.
- ✓ CAZ-AVI was more active than currently available B-lactams, including organisms that are resistant to most currently available agents, such as CRE and MDR P. aeruginosa strains .