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In Vitro Activity of Cefepime-Taniborbactam and Comparator Agents Against Gram-Negative Bacteria Isolated from Patients with Cancer

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Background:

The incidence of Gram-negative (GN) bacterial infections has been increasing in patients with cancer underscoring the critical need for innovative therapeutic interventions to particularly target the emergence of the most concerning multidrug-resistant (MDR) GN pathogens. Taniborbactam, is a β-lactamase inhibitor (βLI), that when combined with cefepime (FEP), may offer a potential treatment option for patients with serious GN bacterial infections. This study aimed to evaluate the *in vitro* activity of a novel combination of cefepime-taniborbactam (FTB) and compare it to other antibiotics active against recent GN bacterial pathogens isolated from patients with cancer (PWC) at our institution.

Material and Methods:

Recent 270 GN clinical isolates from cancer patients were tested against FTB and comparators. CLSI approved broth microdilution method was used. Appropriate ATCC controls were included. MIC_{50}, MIC_{90}, and percent of susceptibility calculations were made using CLSI breakpoints when available. Statistical analysis was used using Fisher exact test (significance at $P \leq 0.05$).

Comparative Susceptibility (%) of cefepime-taniborbactam and comparators against GNB including highly resistant pathogens isolated from patients with cancer

Species	#No.	FTB ##No. (S:%)	FEP ##No. (S:%)	CZA ##No. (S:%)	C/T ##No. (S:%)	MEM ##No. (S:%)	TZP ##No. (S:%)	LVX ##No. (S:%)	AMK ##No. (S:%)
**ESBL *E coli*	20	**20 (100)**	**1 (5)**	**20 (100)**	**17 (85)**	**20 (100)**	**9 (45)**	**2 (10)**	**20 (100)**
p-value*			<0.0001	NA	NS	NA	0.0001	<0.0001	NA
CRE- *E coli*	10	**8 (80)**	**0 (0)**	**5 (50)**	**2 (20)**	**3 (30)**	**1 (10)**	**0 (0)**	**6 (60)**
p-value*			<0.001	NS	0.023	NS	0.006	<0.001	NS
ESBL- *K. pneumoniae*	25	**25 (100)**	**2 (8)**	**25 (100)**	**10 (40)**	**25 (100)**	**7 (28)**	**8 (32)**	**25 (100)**
p-value*			<0.0001	NA	<0.0001	NA	<0.0001	<0.0001	NA
CRE- *K. pneumoniae*	20	**20 (100)**	**0 (0)**	**16 (80)**	**0 (0)**	**3 (15)**	**3 (15)**	**0 (0)**	**15 (75)**
p-value*			<0.0001	NS	<0.0001	<0.0001	<0.0001	<0.0001	0.047
MDR *P. aeruginosa*	20	**19 (95)**	**0 (0)**	**14 (70)**	**13 (65)**	**2 (10)**	**5 (25)**	**0 (0)**	**13 (65)**
p-value*			<0.0001	NS	0.044	<0.0001	<0.0001	<0.0001	0.044
Stenotrophomonas maltophilia	30	**30 (100)**	**0 (0)**	**10 (33.3)**	**4 (13.3)**	**0 (0)**	**0 (0)**	**17 (56.7)**	**8 (26.7)**
p-value*			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Total of resistant isolates	125	**122 (97.6%)**	**3 (2.4%)**	**90 (72.0%)**	**46 (36.8%)**	**53 (42.4%)**	**25 (20.0%)**	**27 (21.6%)**	**87 (69.6%)**
p-value*			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
GNB other than resistant isolates	145	**145 (100.0%)**	**104 (71.7%)**	**143 (98.6%)**	**122 (84.1%)**	**136 (93.8%)**	**82 (56.6%)**	**111 (76.6%)**	**144 (99.3%)**
p-value*			<0.0001	NS	<0.0001	0.003	<0.0001	<0.0001	NS
Total (of all tested isolates)	**270**	**267 (98.9%)**	**107 (39.6%)**	**233 (86.3%)**	**168 (62.2%)**	**191 (70.7%)**	**107 (39.6%)**	**138 (51.1%)**	**231 (85.6%)**
p*-value			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Abbreviations:
FTB= Cefepime-taniborbactam; **AMK**= Amikacin; **FEP**= Cefepime; **CZA**= Ceftazidime-avibactam; **C/T**, Ceftolozane-tazobactam; **MEM**= Meropenem; **TZP**= Piperacillin-tazobactam; **LVX**= Levofloxacin; **ESBL**= Extended Spectrum β-Lactamase; **CRE**= Carbapenem-resistant Enterobacterales; **MDR** = Multi-drug resistance; **NS**=Non-significant (***p>0.05***); **NA**= Non-applicable as no statistics is computed because the variable has only one level.
Notes: **#No**=Number of tested isolates; **##No. (S:%)** = Number of susceptible isolates (Percent of susceptibility); **** P-value*** is from Fisher's exact test comparing the corresponding comparator with FTB.

Results:

- FTB demonstrated highly potent activity against all tested Enterobacterales including ESBL, and CRE as well as against *P. aeruginosa* including MDR isolates, and *Stenotrophomonas maltophilia.*
- At a provisional breakpoint of ≤ 16/4 µg ml-1, FTB inhibited all tested species of Enterobacterales with overall 98.9% susceptibility while it was ranged from 39.6% to 86.3% for cefepime (FEP), and ceftazidime-avibactam (CZA) respectively with highly significant differences ($P < 0.0001$) between FTB and all tested comparators.

Conclusions:

- Our data demonstrates that the FTB combination has promising activity against GN bacterial pathogens isolated from PWC including MDR, CRE and ESBL isolates.
- Taniborbactam as βLI in a combination with FEP showed activity against 98.9% of tested GN bacterial isolates, in contrast to other BL/BLI combinations that exhibited lower activity than cefepime-taniborbactam.
- Further studies are warranted to compare FTB to other BL/BLI combinations against virulent organisms expressing serine, and metallo- β-lactamase.