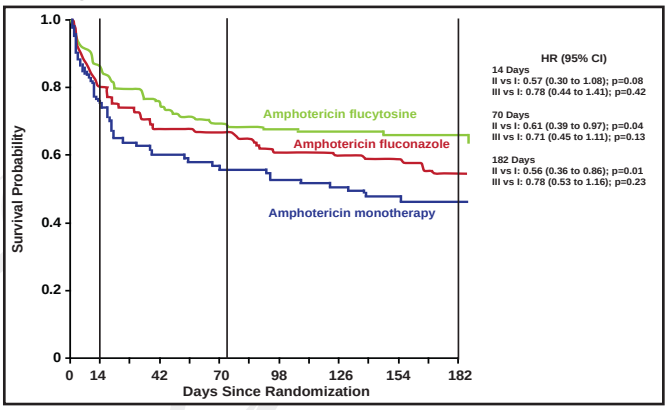
no survival advantage compared with amphotericin monotherapy. After adjusting for fungal burden and Glasgow coma score at study entry, the hazard of death by 6 months was also significantly higher among amphotericin-fluconazole-treated patients versus those who received amphotericin-flucytosine (adjusted HR for all-cause mortality, 1.81; 95% CI, 1.14 to 2.88; p=0.01). The death rate at 70 days was 30% for patients who were on combination therapy with flucytosine versus 44% for those who were on monotherapy. Rates of adverse events between the two combination regimens were comparable and included anemia, neutropenia, and renal impairment.

Figure 1. Kaplan-Meier Curve of Survival Outcomes Among ITT Population.



Significantly improved survival noted among patients treated with flucytosine-containing combination therapy (Arm II, green line) compared with amphotericin monotherapy (Arm I, blue line) at 70 days and 182 days.
Reproduced with permission from J. Day, MD.

Dr. Day concluded by saying that in light of this research, improving access to amphotericin and flucytosine in regions where cryptococcal disease is prevalent, such as southeast Asia and Africa, has the potential to significantly reduce the global burden of deaths due to this devastating disease.

CXA-201 Effective Against Common ICU Pathogens, Including MDR Gram-Negative Pathogens and *Pseudomonas aeruginosa*

Written by Eric Butterman

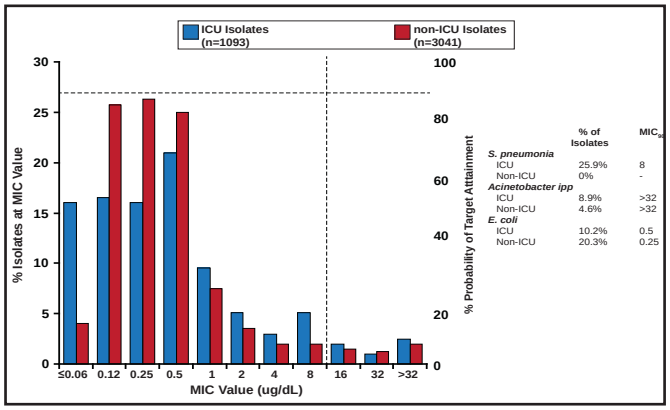
Using a pharmacokinetic/pharmacodynamic (PK/PD) target algorithm, the *in vitro* potency of CXA-201 (CXA101/tazobactam), a novel cephalosporin and β-lactamase inhibitor combination that is being developed to treat serious bacterial infections, was reported to be lower in isolates from the intensive care unit (ICU) compared with non-ICU isolates. This is largely driven by the differences in pathogen incidence in the two environments. Judith Steenbergen, PhD, Cubist Pharmaceuticals, Lexington, Massachusetts, USA, presented data from a study that evaluated the CXA-201 potency for pathogens that were isolated from ICU and non-ICU patients. In addition, the potency of CXA-201 against isolates from different sources of infection was evaluated.

CXA-201 is active against gram-negative pathogens, including *Pseudomonas aeruginosa* and *Enterobacteriaceae*, and select gram-positive organisms. The PK/PD parameter that was used in this study to predict efficacy was the time that was necessary to maintain concentrations of CXA-201 above the minimum inhibitory concentration (MIC) for approximately 40% to 50% of the time between dose administrations (T>MIC).

CXA-201 was tested by broth microdilution against 4134 isolates that were collected in 2008 from both ICU (n=1093) and non-ICU (n=3041) patients. A population PK model that was derived from healthy volunteers and infected patients was used to perform the Monte Carlo simulations (taking into account variability between subjects, residual variability, demographic covariates, and MIC). Target attainment rates were obtained for 1-hour infusion of 1500 mg CXA-201 every 8 hours. For pathogens with an MIC of 8 µg/mL (cutoff target), the target attainment rate was 98.2% for 40% T>MIC.

MIC_{90} was higher for isolates from the ICU (MIC_{90} =8 µg/mL) than non-ICU isolates (MIC_{90} =2 µg/mL). This was largely driven by differences in the percentage of *Streptococcus pneumoniae*, *Acinetobacter spp.*, and *Escherichia coli* isolates in the ICU versus non-ICU patients (Figure 1).

Figure 1. Potency of CXA-201 for ICU and Non-ICU Isolates.



Reproduced with permission from J. Steenbergen, PhD.

More than 95% of all isolates had an MIC ≤8 µg/mL (8 µg/mL being the provisional breakpoint), with a

range of 68% (*Acinetobacter spp.*) to 100% (*Haemophilus influenzae*). When CXA-201 potency was analyzed by site of infection, approximately 95% of all isolates had an MIC ≤8 µg/mL, with a range of 94% (blood) to 96.9% (urine).

Whether sorted by site or source, approximately 95% of isolates had an MIC value <8 µg/mL. All pathogens had an MIC_{90} ≤8 µg/mL except *Enterobacter cloacae* (88% inhibited at ≤8 µg/mL) and *Acinetobacter spp.* (68.5% inhibited at ≤8 µg/mL). Thus, CXA-201 is predicted to achieve excellent target attainment of 40% T>MIC against common ICU pathogens and multidrug-resistant gram-negative pathogens, including *P. aeruginosa* (99.3% inhibited at ≤8 µg/mL).

Tigecycline Plus Standard Therapy Is More Effective Than Standard Therapy Alone For Treating Infections in Febrile Neutropenic Cancer Patients

Written by Eric Butterman

Tigecycline, first in a new class of glycylcyclines, in combination with piperacillin/tazobactam, is effective, safe, and well tolerated in high-risk febrile neutropenic oncohematologic patients. Giampaolo Bucaneve, MD, University of Perugia, Perugia, Italy, believes that tigecycline in combination should be considered one of the "first-line" empiric antibiotic therapies (particularly in a specific epidemiological setting (eg, high rate of extended-spectrum β-lactamase-producing gram-negatives and/or methicillin-resistant *Staphylococci*). This combination therapy may aid in reducing the increase and extensive use of carbapenems, which have been associated with an increase in multidrug-resistant bacteria.

This prospective, randomized, multicenter study included 364 cancer patients from 28 Italian oncohematological departments with profound (<500 neutrophils/mmc) chemotherapy-induced neutropenia and fever (>38.5°C once or >38°C on at least two occasions during a period of 12 hours) due to presumed infection. Patients were randomized centrally and stratified according to center and underlying disease (acute leukemia vs lymphoma and solid tumors). Patients received either IV (n=174) piperacillin/tazobactam (4.5 g 3x daily) plus tigecycline (50 mg twice daily) or IV (n=190) piperacillin/tazobactam (4.5 g 3x daily) as monotherapy. All other antibiotic therapy was stopped at randomization.

Successful treatment was defined as resolution of fever (maintained for at least 4 days) or any clinical sign of infection whenever present and eradication of the infecting microorganism whenever isolated, without change in the initial allocated treatment. Failure was defined as one of the following: death from primary infection, persistence of bacteremia beyond the first 24 hours of therapy, breakthrough bacteremia, documented pathogen resistant to assigned antibiotic(s), lack of response that required antibacterial therapy modification, development of shock or acute respiratory distress syndrome or disseminated intravascular coagulation or multiple organ failure, relapse of infection within 7 days of treatment discontinuation, or toxicity requiring treatment discontinuation.

Overall response to therapy was significantly ($p<0.01$) more effective following piperacillin/tazobactam plus tigecycline (72%) compared with monotherapy (47%; Table 1). Piperacillin/tazobactam plus tigecycline treatment success rates were significantly ($p\leq0.01$) greater for microbiologically (with bacteremia) and clinically documented infections compared with monotherapy. Single gram-positive and -negative (*E. coli*) bacteremias and coagulase-negative *Staphylococcus* species were more successfully treated with combination therapy than monotherapy (Table 2).

Table 1. Classification of Febrile Episodes and Response To Therapy.

Type of infection	Piperacillin/ tazobactam + tigecycline*	Piperacillin/ tazobactam*	p value
Total febrile episodes	174	190	
Microbiologically documented infections	54/88 (61%)	27/96 (28%)	<0.01
with bacteremia	52/86 (60%)	26/94 (27%)	<0.01
without bacteremia	2/2 (62%)	1/2 (25%)	0.5
Clinically documented infections	16/19 (84%)	9/19 (47%)	0.01
Unexplained fever	56/67 (83%)	54/75 (72%)	0.07
Total	126/174 (72%)	90/190 (47%)	<0.01

*success/total

Table 2. Agents of Bacteremias and Antibiotic Susceptibility.

Organism	Tigecycline*	Piperacillin/ tazobactam*
Total Gram-positives	80/89 (90%)	23/94 (24%)
Total Gram-negatives	53/66 (80%)	45/71 (63%)
Coagulase-negative *Staphylococcus*	54/58 (93%)	4/62 (6.5%)