A Prospective Randomized Study Comparing Ceftolozane/Tazobactam to Standard of Care in the Management of Neutropenia and Fever in Patients with Hematological Malignancies

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Key points: Ceftolozane/tazobactam can be used as empiric treatment in cancer patients with neutropenia and fever. It is safe and is associated with better clinical outcomes compared to other standard of care antimicrobial agents.
ABSTRACT

**Background.** With increased use of antibiotics in high risk patients, the investigation of new antibiotics to cover potentially resistant pathogens is warranted. In this prospective randomized trial (NCT03485950), we compared ceftolozane/tazobactam (C/T), a new cephalosporin/β-lactamase inhibitor, to the standard-of-care (SOC) for the empiric treatment of neutropenia and fever in patients with hematological malignancies.

**Methods.** We enrolled 100 patients to receive intravenous (IV) C/T or SOC antibiotics (cefeipime, piperacillin/tazobactam, or meropenem) in combination with gram-positive antibacterial agents. We evaluated responses at the end of IV therapy (EOIV), test of cure (TOC; days 21-28), and late follow-up (LFU; days 35-42).

**Results.** We analyzed 47 C/T patients and 50 SOC patients. C/T patients had a higher rate of favorable clinical response at EOIV (87% vs 72%). A one-sided non-inferiority analysis indicated that C/T was at least not inferior to the SOC for favorable clinical response at EOIV (p=0.002), TOC (p=0.004) and LFU (p=0.002). Superiority tests showed that C/T led to significantly lower rates of clinical failure at TOC (6% vs 30%; p=0.003) and LFU (9% vs 30%; p=0.008). C/T and SOC patients with documented infections had similar rates of favorable microbiological response. Serious adverse events leading to drug discontinuation (2% vs 0%; p=0.48), and overall mortality (6% vs 4%; p=0.67) were similar in both groups.

**Conclusions.** The empiric use of C/T in high-risk patients with hematological malignancies and febrile neutropenia is safe and associated with better clinical outcomes than SOC antimicrobial agents.

**Keywords:** cancer patients, febrile neutropenia, neutropenic fever, neutropenia, fever, immunocompromised, leukemia
INTRODUCTION

Patients with hematologic malignancies (HM) and recipients of hematopoietic stem cell transplantsations (HSCT) receive intensive chemotherapy that often induces prolonged neutropenia, which puts these patients at particularly high risk for potentially life-threatening infections particularly if not recognized and treated promptly. Delaying appropriate antibiotic therapy in patients with *P aeruginosa* BSIs or other resistant gram negatives has been associated with poor outcomes and increase mortality.

The careful evaluation of these patients’ signs and symptoms, antimicrobial prophylaxis, prior infections, previous antimicrobial use, and potential antimicrobial resistance is crucial to guide the appropriate selection of antimicrobial therapy. Although only 20-30% of patients with neutropenia and fever have a clinically or microbiologically documented infection, the rate of infections caused by gram-negative pathogens is increasing with the emergence of antimicrobial-resistant strains.

Hence, standard empirical therapy with cefepime, piperacillintazobactam, or carbapenems could be inappropriate for cancer patients with FN, particularly those with a history of infection or colonization with an antibiotic-resistant organism (such as extended-spectrum B-lactamase (ESBL) producing Enterobacteriaceae or resistant Pseudomonas). Any initial empirical antibiotic therapy given for febrile neutropenia (FN) should include an antipseudomonal B-lactam agent to cover the most virulent and resistant gram-negative pathogens. Antibiotics against gram-positive pathogens should be added for suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. If antimicrobial resistance is suspected, the addition of other antimicrobials should be considered, particularly if the patient is hemodynamically unstable.

Despite successful antibiotic stewardship programs, antibiotic resistance continues to emerge, particularly in patients with gram-negative bacterial infections. Ceftolozane/tazobactam (C/T), a combination of a novel antipseudomonal cephalosporin antibiotic and an established β-lactamase inhibitor, was initially developed to address antimicrobial resistance in cases of serious infections caused by gram-negative pathogens. The addition of tazobactam extends the spectrum...
of C/T coverage to include ESBL producing Enterobacteriaceae. C/T is now approved in the United States for the treatment of complicated intra-abdominal infections in combination with metronidazole; complicated urinary tract infections, including pyelonephritis; and ventilated nosocomial pneumonia.\textsuperscript{16-19} Few case reports have reported promising results with favorable outcomes in HM and HCST patients with FN and Pseudomonas aeruginosa infections or other resistant gram negative organisms.\textsuperscript{20-22} However, the empiric use of C/T for the treatment of FN has not been evaluated in a prospective randomized trial. In this study, we compared C/T with standard-of-care (SOC) antibiotics (cefepine, meropenem or piperacillin/tazobactam) given with anti-gram-positive antibiotics for the empiric treatment of FN in patients with HM.

METHODS

Study Design

This single-center, prospective, randomized, open-label comparative study was approved by our Institutional Review Board and is registered at ClinicalTrials.gov (NCT03485950). Written informed consent was obtained from all patients or their authorized representatives.

Patient Population

Eligible patients were age ≥18 years, had MH, presented to our emergency center with FN, and required hospitalization for intravenous (IV) empiric antibiotic therapy. Patients were excluded if they were allergic to any cephalosporin antibiotic, previously received IV antibiotics for >24 hours, had a confirmed viral or fungal infection, alanine aminotransferase level >5 times the upper limit of normal (ULN), total bilirubin level >3 times the ULN, creatinine clearance ≤ 30 ml/min, or a history of seizure disorder.
Randomization, Treatment, and Monitoring

Between May 2018 and October 2020, 100 patients were enrolled and randomized using our institutional Clinical Trial Conduct web site to receive either C/T (1.5 g every 8 hours) or SOC antibiotics (cefepime [2 g every 8 hours], meropenem [1 g every 8 hours], or piperacillin/tazobactam [4.5 g every 6 hours], at the discretion of the treating physician) for at least 72 hours and up to 14 days.

Patients in either group could receive antibacterial agents (vancomycin, linezolid, or daptomycin) for gram-positive infections if indicated for suspected line infection, skin and soft tissue infection, pneumonia, hemodynamic instability, history of methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci colonization, or severe mucositis, according to the Infectious Diseases Society of America (IDSA) clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer.\(^2\) The choice and duration of gram-positive coverage was determined by the treating physician.

Early de-escalation after 72 hours was encouraged and implemented if appropriate after assessing the patient and reviewing the culture results as an antimicrobial stewardship practice and as pre-determined in the protocol. A switch to oral or narrower spectrum or a once-daily IV agent against gram-negative pathogens for the purposes of outpatient treatment was allowed after 72 hours. The original IV randomized treatment could have been discontinued either as 1) de-escalation (in patients who improved and became afebrile) or 2) due to insufficient therapeutic effect including incomplete clinical resolution or persistence of fever, that requires alternative antimicrobial therapy. The investigator or treating physician was encouraged to continue study therapy[ies] for at least 72 hours before considering such patient as a clinical failure and prematurely discontinuing study therapy[ies]. Patients who were switched prior to 72 hours for reasons other than study drug-related adverse events or resistant organisms were considered as indeterminate. The decision to de-escalate were made by either the investigator or the treating physician who were not blinded to treatment arm. Empirical treatment of \textit{C. difficile} with oral vancomycin or with IV or oral
metronidazole could be added at any time for patients with symptoms of abdominal cramping and diarrhea or if *C. difficile* infection was strongly suspected clinically.

Patients were followed through the end of IV therapy (EOIV). Patients were evaluated 21–28 days after starting IV antibiotic therapy for test of cure (TOC) and 35–42 days after starting therapy as a late follow-up (LFU) (Figure 1). Clinical and microbiological responses were assessed at EOIV, TOC, and LFU.

All patients were monitored throughout the study period, including the 30 days after the last study drug dose, for the development of adverse events (AEs), serious AEs (SAEs), and study drug–related AEs.

**Analysis Populations and Outcomes**

The analysis sets included efficacy and safety analyses and are shown in Figure 2.

The efficacy analysis included clinical and microbiological responses and was based on the modified intent-to-treat (MITT) and microbiological MITT (mMITT) analysis sets.

The primary objective of the study was to show that the efficacy of C/T plus vancomycin, daptomycin, or linezolid is non-inferior to the SOC plus vancomycin, daptomycin, or linezolid as empiric therapy in cancer patients with FN with respect to favorable clinical response. The primary efficacy parameter was the proportion of patients in the MITT analysis set with favorable clinical response at EOIV.

The safety analysis set included all randomized patients who received any amount of IV inpatient study drug. Safety was assessed by assessing AEs and SAEs that were attributed to the study drug throughout the study as well as 30-day mortality.

The secondary efficacy parameters included the proportion of patients in the mMITT and CE analysis sets with favorable clinical response at EOIV; the proportion in the MITT analysis set with favorable clinical response at TOC and LFU; the proportion in the mMITT and clinically evaluable analysis sets with favorable clinical response by baseline gram-negative pathogen at EOIV, TOC, and
LFU; the proportion in the mMITT and ME analysis sets with a favorable microbiological response (defined as eradication or presumed eradication of the infecting pathogen) by baseline gram-negative pathogen at EOIV, TOC, and LFU; the proportion in the MITT and mMITT analysis sets with infection-related mortality at TOC and LFU; as well as 30-day all-cause mortality.

Definitions

FN was defined as either a single oral temperature measurement of ≥101°F (38.3°C) or a temperature of ≥100.4°F (38.0°C) sustained over a 1-hour period, with an absolute neutrophil count (ANC) of <500 cells/ml.

A favorable clinical response was defined as the resolution of all acute signs and symptoms (mainly fever resolution as fever may represent the only sign of infection in patients with neutropenia who may have decreased inflammatory response) of the primary infection at EOIV, TOC, and LFU.

A clinical failure was defined as a fever persisting 96 hours after the initiation of the study drug; discontinuation of study drug after at least 72 hours due to insufficient therapeutic effect including persistence, incomplete clinical resolution, or worsening in signs and symptoms (mainly fever) that requires alternative antimicrobial therapy; a documented breakthrough gram-negative bloodstream infection (BSI); (ie, a recurrent BSI or a new BSI with a gram-negative pathogen not present at baseline but occurring while on study drug); a documented study drug–resistant gram-negative pathogen that required alternative antimicrobial therapy; the discontinuation of study drug therapy owing to an AE and the requirement for alternative antimicrobial; death resulting from the primary infection; or >1 therapy switch after the discontinuation of the original IV treatment.

Another episode of FN during the follow-up period was not considered a clinical failure unless the patient presented with a relapse of the same documented infection that was present at baseline.

The clinical outcome was classified as indeterminate in any of the following: patient developed a documented invasive fungal or viral infection at any time during the study; patient has a
documented infection with gram-positive organisms; study data were not available for evaluation of
efficacy for any reason including death in which FN was clearly noncontributory or patient was lost
to follow-up; or patient withdrew from the study for reasons other than clinical failure.

In patients with microbiologically documented infections, microbiological response was
defined as either eradication of the original baseline pathogen; presumed eradication (no available
culture and the clinical response assessed as a cure); persistence; presumed persistence (no
available culture and the clinical response assessed as a failure); or as indeterminate (no culture and
the clinical response assessed as indeterminate).

Statistical Analysis
Continuous and categorical variables were summarized by treatment group using descriptive
statistics (medians and ranges) and frequency distributions (counts and percentages), respectively.
Summaries were provided for all randomized patients who received any amount of inpatient IV
study drug (MITT analysis set), and efficacy summaries were provided for the subgroup of patients
with a gram-negative pathogen identified (mMITT analysis set) and other subgroups including
patients in CE analysis set and ME analysis set defined by the protocol (Figure 2). Chi-square or
Fisher’s exact test was used to compare categorical variables, and Wilcoxon rank-sum test was used
to compare continuous variables. One-sided chi-square test for non-inferiority was performed for
the primary endpoint (favorable clinical response) with a non-inferiority margin of 10%. If a non-
inferiority was found, then two-sided chi-square test for superiority was performed for a further
comparison. All the tests were at the significance level of 0.05 and most of them except the non-
inferiority tests were two-sided. The statistical analyses were performed using SAS version 9.3 (SAS
Institute Inc., Cary, NC).
RESULTS

Patient Characteristics

Among the 100 patients enrolled and randomized during the study period, 97 patients (47 in the C/T group and 50 in the SOC group) received at least one dose of the study drug. Three C/T patients withdrew consent before receiving any dose of the study drug and were excluded from the analysis.

The patients’ characteristics are shown in Table 1. The C/T and SOC groups did not differ significantly in terms of age, gender, race, underlying disease, hospital stay duration, ICU admission, or requirement for mechanical ventilation. Antibiotic prophylaxis received before the onset of FN was similar in both arms (81% in C/T vs 90% in SOC arm, \( p=0.2 \)). The main antibiotics given as prophylaxis consisted of fluoroquinolones (82%), followed by cefpodoxime (12%), then others such as amoxicillin, trimethoprim/sulfamethoxazole, cefdinir, etc.. The C/T and SOC groups had similar rates of microbiologically documented infections at baseline, most commonly BSI (28% and 24%, respectively; \( p=0.68 \)). The groups also had similar rates of isolated gram-negative and -positive pathogens. The 6 patients with documented infections caused by gram-negative pathogens at baseline included 3 C/T patients with BSIs, 1 C/T patient with a urinary tract infection, and 2 SOC patients with BSIs. Isolated pathogens included *Escherichia coli* (1 C/T patient and 2 SOC patients), *Pseudomonas aeruginosa* (2 C/T patients), and *Klebsiella pneumonia* (1 C/T patient). Two of the isolated gram-negative pathogens—one *E coli* in the SOC group and one *K pneumonia* in the C/T group, neither of which was carbapenem-resistant—were classified as extended-spectrum β-lactamase (ESBL)-producing multidrug-resistant organisms (MDROs). Compared to SOC, patients in C/T had at baseline a higher rate of clinically documented infection (34% vs 6%; \( p=0.018 \)) and sepsis (62% vs 30%; \( p=0.002 \)), but a lower rate of unexplained fever (38% vs 70%; \( p=0.002 \)) (Supplementary Table 1). Only one patient in C/T, who had a clinically documented infection (pneumonia), had an ICU admission related to his FN episode. The median study drug duration of the C/T group (3 days [range, 1-6]) was shorter than that of the SOC group (4 days [range, 1-14]; \( p=0.11 \)). The SOC group
had a significantly higher rate of patients who received study drugs for >5 days (20% vs 2%; p=0.006).

The group’s treatment regimen characteristics are shown in Supplementary Table 2. In the SOC group, the most commonly used antibiotics were cefepime (76%) followed by piperacillin/tazobactam (20%) and meropenem (4%). In both groups, >90% of the patients received gram-positive coverage, with linezolid being the most commonly used agent. De-escalation at end of IV study drug occurred similarly in both groups (94% in C/T and 84% in SOC; p=0.14), although patients on C/T were more likely to de-escalate to IV study drug compared to SOC (55% vs 21%) (Supplementary Table 3).

Clinical Response
Detailed clinical outcomes are presented in Table 2 and Supplementary Tables 1, 4 and 5. At EOIV, for the MITT population, C/T patients had a higher rate of favorable clinical response than SOC patients did (87% vs 72%). The one-sided non-inferiority analysis indicated that C/T was not inferior to the SOC (p=0.002), which was consistent with the lower limit of the 90% confidence interval (0.013) of their rate difference being greater than the noninferiority limit (-0.10). Moreover, the lower limit of the 95% confidence interval of the difference in the favorable clinical response rates (-0.014) was also greater than the noninferiority limit (-0.10).

At EOIV, C/T patients had lower rates of clinical failure (4% vs 18%) and indeterminate clinical response (9% vs 10%). In both groups, the most common reason for clinical failure at EOIV was persistent fever. One SOC patient required alternative therapy owing to a BSI with E coli that was resistant to the selected study drug (cefepime). It is to note that 76% of patients in the SOC arm received cefepime and 20% received piperacillin/tazobactam, whereas only 4% received meropenem (supp Table 1).

At TOC, C/T was also found to be non-inferior to the SOC with regard to favorable clinical response (p=0.004). Furthermore, superiority tests showed a significant difference between the
groups’ distributions of clinical outcomes (p=0.01), with the C/T group having a significantly lower rate of clinical failure (6% vs 30%; p=0.003). Analyses of LFU data also yielded similar results, with the C/T group again having a significantly lower rate of clinical failure (9% vs 30%; p=0.008).

The clinical outcomes at EOIV, TOC, and LFU for the mMITT and CE populations are presented in Supplementary Tables 5B and 5C, respectively.

**Microbiological Response**

The C/T and SOC groups’ rates of microbiological response at EOIV, TOC, and LFU among patients who had microbiologically documented infections at baseline did not differ significantly (Table 3 and Supplementary Tables 1, 4 and 5).

The microbiologic responses at EOIV, TOC, and LFU in the mMITT and ME populations are presented in Supplementary Tables 5D and 5E, respectively. In the mMITT population, of the 4 C/T patients with documented infections caused by gram-negative pathogens, 1 had an indeterminate clinical outcome at TOC. This patient had a BSI caused by an ESBL/MDRO *K pneumoniae* that was susceptible to C/T; however, the patient was switched to meropenem <72 hours after initiating therapy. Of the 2 SOC patients with documented infections caused by gram-negative pathogens, 1 had clinical failure owing to a BSI caused by an ESBL/MDRO *E coli* that was resistant to cefepime and required a switch to meropenem <72 hours after initiating therapy with cefepime.

In patients with documented gram-negative infections at baseline, there was no relapse or emergence of gram-negative resistant organisms during the follow-up period. Five patients developed a new bacteremia with a different gram-negative organism that was not present at baseline and that occurred after the end of IV therapy: four in the CT arm and one in the SOC arm.

In the CT arm, four patients developed five episodes of bacteremia after EOIV and during the follow-up period. The recovered isolates consisted of *E Coli* (two patients), *Ps Aeruginosa* (one patient), *K pneumoniae* and *Stenotrophomonas* (one patient). In the SOC arm, one patient developed *E Coli* bacteremia. Except for the stenotrophomonas, none of the isolates were resistant to the
randomized study drugs that they received. The microbiological outcomes of these patients were not considered as failures as the bacteremia occurred after end of IV study drug and not while on study drug.

**Safety**

The C/T and SOC groups’ overall rates of AEs and SAEs did not differ significantly (Table 4). Although the rate of drug-related AEs tended to be higher in C/T group (17% vs 6%, p=0.09), the rate of drug-related SAEs were similar in both groups (2% vs 0%, p=0.48) (Table 4). In addition, the groups’ rates of study drug-related AEs and SAEs that led to drug discontinuation did not differ significantly. The most common study drug-related AEs in the C/T group were increased liver function tests (transaminase and bilirubin levels), rash, increased alkaline phosphatase level, and headache. Both groups had a 30-day mortality rate of 4%, and their rates of mortality during the study did not differ significantly (6% vs 4%; p=0.67). There was no study drug-related death in either group (Table 2 and Supplementary Table 5F-I). All SAEs and non-SAEs, regardless of their attribution, are presented in Supplementary Table 6 and Supplementary Table 7, respectively. Non-SAEs reported with a frequency of at least 5% are presented in Table 5.

**DISCUSSION**

Our findings show that C/T is non-inferior and may be superior to the SOC in patients with HM and FN. In the MITT population, compared with SOC patients, C/T patients not only had a non-inferior rate of favorable clinical response at EOIV, TOC, and LFU but also had a significantly lower rate of clinical failure at TOC and LFU.

In our study, the most commonly used antibiotic in the SOC arm was cefepime (76%) followed by piperacillin/tazobactam (20%) and meropenem (4%). Microbiologically documented infections with either gram-negative or -positive pathogens were identified at baseline in 25% of our
patients and were primarily BSIs (92%), with similar distributions in both groups. Our documented infection rate is similar to those reported previously. Although the rate of gram-negative infections is increasing, gram-negative pathogens were isolated in only 6% of our patients, mostly from blood (83%). Of the 6 patients with documented gram-negative infections, 2 (33%) had an ESBL/MDRO pathogens that required an early switch of the antibiotic <72 hours after initiating therapy.

Given the increasing rate of ESBL-producing gram-negative bacteria, the empiric use of fourth-generation β-lactams such as cefepime or extended-spectrum penicillin/β-lactamases inhibitors such as piperacillin/tazobactam could be suboptimal especially in high risk patients with underlying malignancy and FN. C/T, a combination of a novel cephalosporin and an established β-lactamase inhibitor, could be used as an alternative to carbapenems. C/T has shown in vitro activity against a wide range of gram-negative pathogens, including multidrug-resistant *P. aeruginosa* and ESBL-producing Enterobacteriaceae. The lower rates of clinical failure observed with C/T at TOC and LFU remains unclear given the very low number of documented gram-negative MDRO.

In this study we used the C/T limited dose of 1.5 gm every 8 hours given that the 3gm dose was still considered investigational at the time of registration of this study. The 3-gm dose has since been approved by the FDA for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia and should be considered as the preferred dose in patients with FN to empirically cover multidrug-resistant *P. aeruginosa*.

In the present study, the median study drug duration of the C/T group (3 days) was shorter than that of the SOC group (4 days; p=0.08). Only 1 C/T patient (2%) but 10 SOC patients (20%) received study drugs for >5 days (p=0.006). This difference could be due to the early de-escalation procedures that were implemented after the patients’ clinical improvement which occurred earlier and more frequently in the C/T arm.

Both the C/T and SOC groups had high rates of AEs and SAEs that were equally distributed, which reflects the complexity of this severely immunocompromised patient population. Although
C/T patients tended to have a higher rate of study drug–related AEs, both groups had relatively few study drug–related AEs and SAEs that led to drug discontinuation.

This is the first randomized controlled trial that evaluated the safety and efficacy of C/T in high-risk patients with HM and FN. Our study had several limitations. The study enrolled eligible patients, including those without a history of an ESBL-producing organism or an MDRO. However, such patients are severely immunosuppressed and are frequently hospitalized for complications resulting from their intensive chemotherapy. In addition, the study included very few patients with documented gram-negative pathogens. Another limitation is the open-label design of the study which could have introduced a potential source of bias in the assessment of the patient. Although most of the endpoints were objective based on measurable endpoints such as temperature for the clinical outcome or cultures for microbiologic documentation, the decision to de-escalation or to discontinue study drug and the attribution of the adverse event to study drug may have been biased by the assessor who was not blinded to the treatment agent.

CONCLUSIONS

C/T is efficacious and safe, and its prudent and judicious use should be considered, in the context of local patterns of antibiotic resistance, for the empiric treatment of high-risk patients with HM and FN, particularly those with a history of infection or colonization with resistant gram-negative organisms and/or prior hospitalization and antibiotic overuse. Closely monitoring patients, optimizing antibiotic selection, and reassessing and de-escalating antibiotic treatment using culture results and susceptibility patterns should be implemented to attain the shortest effective duration of therapy and limit the emergence of resistant pathogens.
Notes

Authors’ Contributions. AMC, RH, and IR were responsible for study conception and protocol design. AMC wrote the first draft of the manuscript. AMC, RH, AEM, AS, VM, SA, PC and IR were responsible for patient screening, enrollment and follow-up. SA and RD were responsible for data collection. AMC, RH, SA, RD have verified the underlying data. YJ and YY designed the statistical analysis plan, analyzed the data, and developed the figures and the tables. AMC, RH, and IR were responsible for overall project and data management. All authors had full access to the study data and were responsible for the final decision to submit the manuscript for publication. All authors were responsible for critical review of drafts and approval of the final manuscript.

Data sharing. The study protocol, statistical analysis plan, lists of deidentified individual data, and generated tables and figures will be made available upon request by qualified scientific and medical researchers for legitimate research purposes. Requests should be sent to achaftari@mdanderson.org and yijiang@mdanderson.org. Data will be available on request for 6 months from the date of publication. Investigators are invited to submit study proposal requests detailing research questions and hypotheses in order to receive access to these data.

Potential Conflicts of interests. The authors have no competing interests to declare.

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1. Zuckermann J, Moreira LB, Stoll P, Moreira LM, Kuchenbecker RS, Polanczyk CA. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. Ann Hematol. Feb 2008;87(2):139-145.

2. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. Feb 15 2011;52(4):e56-93.

3. Lodise TP, Jr., Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with Pseudomonas aeruginosa bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother. Oct 2007;51(10):3510-3515.

4. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. Pseudomonas aeruginosa bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother. Apr 2005;49(4):1306-1311.

5. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. J Antimicrob Chemother. Jun 2012;67(6):1311-1320.

6. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, et al. Inappropriate Empirical Antibiotic Treatment in High-risk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance. Clin Infect Dis. Mar 3 2020;70(6):1068-1074.

7. Gudiol C, Albasanz-Puig A, Laporte-Amargos J, et al. Clinical Predictive Model of Multidrug Resistance in Neutropenic Cancer Patients with Bloodstream Infection Due to Pseudomonas aeruginosa. Antimicrob Agents Chemother. Mar 24 2020;64(4).

8. Trecarichi EM, Tumbarello M. Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: current epidemiology and clinical impact. Curr Opin Infect Dis. Apr 2014;27(2):200-210.

9. Irfan S, Idrees F, Mehrjoo V, Habib F, Adil S, Hasan R. Emergence of Carbapenem resistant Gram negative and vancomycin resistant Gram positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study. BMC Infect Dis. Jun 9 2008;8:80.

10. Montassier E, Batard E, Gastinne T, Potel G, de La Cochetiere MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis. Jul 2013;32(7):841-850.

11. Pagano L, Caira M, Rossi G, et al. A prospective survey of febrile events in hematological malignancies. Ann Hematol. May 2012;91(5):767-774.

12. Hansen BA, Wendelbo O, Bruserud O, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. Mediterr J Hematol Infect Dis. 2020;12(1):e2020009.

13. Cluck D, Lewis P, Stayer B, Spivey J, Moorman J. Ceftolozane-tazobactam: A new-generation cephalosporin. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. Dec 15 2015;72(24):2135-2146.

14. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-ciAI). Clin Infect Dis. May 15 2015;60(10):1462-1471.
17. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet (London, England)*. May 16 2015;385(9981):1949-1956.

18. Lucasti C, Hershberger E, Miller B, et al. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. *Antimicrob Agents Chemother*. Sep 2014;58(9):5350-5357.

19. Kollef MH, Novacek M, Kivistik U, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. Dec 2019;19(12):1299-1311.

20. Fernandez-Cruz A, Alba N, Semiglia-Chong MA, et al. A Case-Control Study of Real-Life Experience with Ceftolozane-Tazobactam in Patients with Hematologic Malignancy and Pseudomonas aeruginosa Infection. *Antimicrob Agents Chemother*. Feb 2019;63(2).

21. Hakki M, Lewis JS, 2nd. Ceftolozane-tazobactam therapy for multidrug-resistant Pseudomonas aeruginosa infections in patients with hematologic malignancies and hematopoietic-cell transplant recipients. *Infection*. Jun 2018;46(3):431-434.

22. Clerici D, Oltolini C, Greco R, et al. The place of ceftazidime/avibactam and ceftolozane/tazobactam for therapy of haematological patients with febrile neutropenia. *Int J Antimicrob Agents*. Jun 2021;57(6):106335.

23. Klastersky J, Ameye L, Maertens J, et al. Bacteraemia in febrile neutropenic cancer patients. *Int J Antimicrob Agents*. Nov 2007;30 Suppl 1:S51-S59.

24. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and Pseudomonas aeruginosa with various resistance patterns isolated in U.S. Hospitals (2011-2012). *Antimicrob Agents Chemother*. Dec 2013;57(12):6305-6310.

25. Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against Pseudomonas aeruginosa and Enterobacteriaceae with various resistance patterns isolated in European hospitals (2011-12). *J Antimicrob Chemother*. Oct 2014;69(10):2713-2722.

26. Sader HS, Farrell DJ, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against aerobic Gram-negative organisms isolated from intra-abdominal and urinary tract infections in European and United States hospitals (2012). *J Infect*. Sep 2014;69(3):266-277.

27. Walkty A, Karlowsky JA, Adam H, et al. In vitro activity of ceftolozane-tazobactam against Pseudomonas aeruginosa isolates obtained from patients in Canadian hospitals in the CANWARD study, 2007 to 2012. *Antimicrob Agents Chemother*. Nov 2013;57(11):5707-5709.

28. Sutherland CA, Nicolau DP. Susceptibility Profile of Ceftolozane/Tazobactam and Other Parenteral Antimicrobials Against Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa From US Hospitals. *Clinical Therapeutics*. Jul 1 2015;37(7):1564-1571.

29. Tato M, Garcia-Castillo M, Bofarull AM, Canton R. In vitro activity of ceftolozane/tazobactam against clinical isolates of Pseudomonas aeruginosa and Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study. *Int J Antimicrob Agents*. Nov 2015;46(5):502-510.

30. Estabrook M, Bussell B, Clugston SL, Bush K. In vitro activity of ceftolozane-tazobactam as determined by broth dilution and agar diffusion assays against recent U.S. Escherichia coli isolates from 2010 to 2011 carrying CTX-M-type extended-spectrum beta-lactamas. *Journal of clinical microbiology*. Nov 2014;52(11):4049-4052.
Figure Legends

**Figure 1.** Study design.

**Figure 2.** Patient population and analysis sets.
Table 1. Characteristics of Patients Who Received Ceftolozane/Tazobactam and Those Who Received the Standard of Care.

| Characteristic                        | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) | p-value |
|---------------------------------------|--------------------------------|-------------------------|---------|
| Age, median (range), years            | 60 (25-84)                     | 55 (18-79)              | 0.12    |
| Sex                                   |                                |                         | 0.65    |
| Male                                  | 28 (60)                        | 32 (64)                 |         |
| Female                                | 19 (40)                        | 18 (36)                 |         |
| Race                                  |                                |                         | 0.85    |
| White                                 | 32 (68)                        | 35 (70)                 |         |
| Black                                 | 4 (9)                          | 5 (10)                  |         |
| Hispanic                              | 6 (13)                         | 7 (14)                  |         |
| Asian                                 | 0 (0)                          | 1 (2)                   |         |
| Middle Eastern                        | 3 (6)                          | 1 (2)                   |         |
| Others                                | 2 (4)                          | 1 (2)                   |         |
| Hematological malignancy              |                                |                         | 0.32    |
| ALL                                   | 9 (19)                         | 12 (24)                 |         |
| AML                                   | 19 (40)                        | 22 (44)                 |         |
| CML                                   | 3 (6)                          | 0                       |         |
| Lymphoma                              | 9 (19)                         | 6 (12)                  |         |
| Others                                | 7 (15)                         | 10 (20)                 |         |
| BMT within 1 year prior to fever      | 6 (13)                         | 9 (18)                  | 0.48    |
| Autologous                            | 2/6 (33)                       | 4/9 (44)                |         |
| Allogeneic                            | 4/6 (67)                       | 5/9 (56)                |         |
| Type of allogeneic transplant | Matched unrelated donor | HLA matched related donor | GVHD |
|------------------------------|-------------------------|--------------------------|------|
|                              | 0                       | 1/5 (20)                 | 1/6 (17) | 1/8 (13) |
| HLA matched related donor    | 4/4 (100)               | 4/5 (80)                 |
| GVHD                         | 37.5 (37.0–37.23)       |

| Temperature at baseline, median (IQR), °C | 37.3 (36.9–38.2) | 38.3 |

| Temperature at initial presentation, °C | <36 | 36–38 | >38 |
|----------------------------------------|-----|-------|-----|
|                                        | 0   | 3 (6) | 44 (94) |
|                                        | 0   | 7 (14) | 43 (86) |

| Microbiological documentation (positivity) | 13 (28) | 12 (24) |

| Site of microorganisms<sup>a</sup> | Genitourinary tract | Blood |
|-----------------------------------|---------------------|-------|
|                                   | 2                   | 11    |
|                                   |                     |       |

| Gram-negative bacterial pathogen | 4 (9) | 2 (4) |

| Gram-negative alone | 2     |

| Gram-negative and -positive (mixed infection) | 2     |

| Organisms recovered in positive cultures<sup>b</sup> | Escherichia coli | Klebsiella pneumoniae | Pseudomonas aeruginosa | MRSA | Rothia mucilaginosa | Streptococcus viridans | Staphylococcus epidermidis |
|-----------------------------------------------------|-----------------|----------------------|-----------------------|------|-------------------|-----------------------|---------------------------|
|                                                     | 0               | 1                    | 1                     | 2    | 1                 | 5                     | 1                         |

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| Pathogen                        | No. | %    |
|--------------------------------|-----|------|
| *Enterococcus faecalis*        | 0   | 2    |
| *E faecalis + E coli*          | 1   | 0    |
| *E faecalis + Paeruginosa*     | 1   | 0    |

CVC the source of BSI isolation: 7/11 (64) vs. 7/12 (58), > 0.99
Hospital stay duration, median (IQR), days: 6 (4-9) vs. 7 (4-11), 0.84
ICU admission: 2 (4) vs. 3 (6), > 0.99
Mechanical ventilation: 2 (4) vs. 1 (2), 0.61

Note. Data are no. of patients (%) unless otherwise indicated.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; BMT, bone marrow transplantation; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; CVC, central venous catheter; BSI, bloodstream infection; ICU, intensive care unit.

*a* One patient had 2 sites of organisms.

*b* Four patients 2 or 3 organisms.
| Clinical Outcome at EOIV | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) | p-value |
|--------------------------|-------------------------------|--------------------------|---------|
| Favorable clinical response | 41 (87) | 36 (72) | 0.10 |
| Clinical failure | 2 (4) | 9 (18) |
| Indeterminate | 4 (9) | 5 (10) |

| Clinical Outcome at TOC | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) | p-value |
|--------------------------|-------------------------------|--------------------------|---------|
| Clinical cure | 34 (72) | 28 (56) | 0.01 |
| Clinical failure | 3 (6) | 15 (30) |
| Indeterminate | 10 (21) | 7 (14) | 0.02 |

| Clinical Outcome at LFU | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) | p-value |
|--------------------------|-------------------------------|--------------------------|---------|
| Clinical cure | 33 (70) | 26 (52) |
| Clinical failure | 4 (9) | 15 (30) |
| Indeterminate | 10 (21) | 9 (18) |

Mortality during the study | 3 (6) | 2 (4) | 0.67 |

Duration between last dose of study drug and death, median (range), days | 17 (15-34) | 29 | 0.77 |
|                                |     |     |
|--------------------------------|-----|-----|
| Infection-related mortality    | 0 (0) | 0 (0) |
| 30-day all-cause mortality     | 2 (4) | 2 (4) |

Note: Data are no. of patients (%) unless otherwise specified.

Abbreviations: EOIV, end of intravenous therapy; TOC, test of cure; LFU, late follow-up; AE, adverse event; IV, intravenous.
Table 3. Microbiological Outcome of Patients Who Received Ceftolozane/Tazobactam and Those Who Received the Standard of Care

| Outcome                          | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) | p-value |
|----------------------------------|-------------------------------|-------------------------|---------|
| Microbiologically documented infection | 13 (28)                       | 12 (24)                 | 0.68    |
| Microbiological response at EOIV |                               |                         | 0.73086 |
| Persistence                      | 1/13 (8)                      | 1/12 (8)                |         |
| Eradication                      | 11/13 (85)                    | 9/12 (75)               |         |
| Presumed eradication             | 0/13 (0)                      | 1/12 (8)                |         |
| Indeterminate                    | 1/13 (8)                      | 1/12 (8)                |         |
| Microbiological response at TOC  |                               |                         | 0.64    |
| Persistence                      | 0/13 (0)                      | 1/12 (8)                |         |
| Eradication                      | 3/13 (23)                     | 2/12 (17)               |         |
| Presumed eradication             | 8/13 (62)                     | 9/12 (75)               |         |
| Indeterminate                    | 2/13 (15)                     | 0/12 (0)                |         |
| Microbiological response at LFU  |                               |                         | 0.33    |
| Persistence                      | 0/13 (0)                      | 1/12 (8)                |         |
| Eradication                      | 2/13 (15)                     | 3/12 (25)               |         |
| Presumed eradication             | 81/3 (62)                     | 8/12 (67)               |         |
| Indeterminate                    | 3/13 (23)                     | 0/12 (0)                |         |
| Relapse                          | 0/12 (0)                      | 0/11 (0)                |         |

Note: Data are no. of patients (%) unless otherwise specified.

Abbreviations: EOIV, end of intravenous therapy; TOC, test of cure; LFU, late follow-up; AE, adverse event; IV, intravenous.
Table 4. Adverse Events (AEs) and Serious AEs (SAEs) of Patients Who Received Ceftolozane/Tazobactam and Those Who Received the Standard of Care

| Event                                | Ceftolozane/Tazobactam | Standard of Care | p-value |
|--------------------------------------|-------------------------|------------------|---------|
|                                      | (n=47)                  | (n=50)           |         |
| Total AEs                            | 38 (81)                 | 37 (74)          | 0.42    |
| Total SAEs                           | 33 (70)                 | 33 (66)          | 0.66    |
| Study drug–related AE                | 8 (17)                  | 3 (6)            | 0.09    |
| ALT increased (>ULN)                 | 2 (4)                   | 1 (2)            |         |
| Bilirubin increased (>1.5 ULN)       | 1 (2)                   |                 |         |
| Rash                                 | 5 (11)                  | 2 (4)            |         |
| Alkaline phosphatase increased (>ULN)| 1 (2)                   |                 |         |
| Headache                             | 1 (2)                   |                 |         |
| Study drug–related SAE               | 1 (2)                   | 0 (0)            | 0.48    |
| Bilirubin increased (>1.5 ULN)       | 1 (2)                   |                 |         |
| Study drug–related AE resulting in drug discontinuation | 2 (4) | 2 (4) | >0.99 |
| ALT increased (>ULN)                 |                         | 1 (2)            |         |
| Bilirubin increased (>1.5 ULN)       | 1 (2)                   |                 |         |
| Rash                                 | 1 (2)                   | 1 (2)            |         |
| Study drug–related SAE resulting in drug | 1 (2) | 0 (0) | 0.48 |
| Discontinuation                                    | Study Drug–Related Mortality | 30-Day All-Cause Mortality |
|---------------------------------------------------|------------------------------|-----------------------------|
| Bilirubin increased (>1.5 ULN)                    | 1 (2)                        | 1 (2)                       |
| Mortality                                         | 3 (6)                        | 2 (4)                       |
| Study drug–related mortality                      | 0                            | 0                           |
| 30-day all-cause mortality                        | 2 (4)                        | 2 (4)                       |

Note: Data are no. of patients (%).

Abbreviation: ALT, alanine aminotransferase; ULN, upper limit of normal
Table 5. Non-Serious Adverse Events with a Frequency Threshold above 5% among Patients Who Received Ceftolozane-Tazobactam and Those Who Received the Standard of Care

| Event                              | Ceftolozane/Tazobactam (n=47) | Standard of Care (n=50) |
|------------------------------------|-------------------------------|-------------------------|
| Total                              | 9 (19)                        | 6 (12)                  |
| ALT elevation (>ULN)               | 3 (6)                         | 3 (6)                   |
| Urinary tract infection            | 3 (6)                         | 0 (0)                   |
| Rash                               | 5 (11)                        | 3 (6)                   |

Note: Events were collected by systematic assessment. Data are no. of patients (%).

Abbreviation: ALT, alanine aminotransferase.
Figure 1

Baseline

Within 24 hours before the first dose of study drug

Treatment

Study days 1-3 (minimal required)

TOD

IF SOC plus additional therapy or deteriorates

Follow-up

Study days 4-14 (until the end of IV therapy)

Study days 15-42

IV, Intravenous; SOC, Standard of Care; TOD, Time of Cure; LFU, late follow-up.
Figure 2

Patients enrolled and randomized
n=100

Intention To Treat
All randomized
n=100

Safety
Measure any amount of in-study drug
n=100

Modified Intent To Treat (MITT)
Randomized and received any amount of in-study drug
n=100

Clinically Evaluable (CE)
For endpoint measurement of drug treatment
Final report of other than bevacizumab at TFC of disease response assessed as a clinical failure at EOT or at any time up to 90 days
n=100

Microbiological Modified Intent To Treat (MMITT)
Any patient receiving baseline bacterial pathogen susceptibility and susceptibility to test drug therapies
n=100

Microbiologically Evaluable (ME)
Meet criteria for both MITT and CE evaluation
n=100

IV, intravenous; EOT, end of IV; TOC, test of cure