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CLINICAL THERAPEUTICS

A Case-Control Study of Real-Life Experience with Ceftolozane-Tazobactam in Patients with Hematologic Malignancy and *Pseudomonas aeruginosa* Infection

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ABSTRACT We present our experience in patients with hematologic malignancy and *Pseudomonas aeruginosa* infection treated with ceftolozane-tazobactam. We performed a single-center case-control study comparing patients with hematologic malignancy and *P. aeruginosa* infection treated with ceftolozane-tazobactam (study group) with similar patients not treated with ceftolozane-tazobactam (control group) to assess safety and efficacy. Nineteen cases and 38 controls were analyzed. Cases were younger (45.6 years versus 57.6 years; $P = 0.012$) and less frequently had bacteremia (52.6% versus 86.8%; $P = 0.008$). They also had worse Multinational Association for Supportive Care in Cancer (MASCC) scores (10.2 versus 16.1; $P = 0.0001$), more hospital-acquired infections (78.9% versus 47.4%; $P = 0.013$), and more extremely drug-resistant (XDR) *P. aeruginosa* infections (47.4% versus 21.1%; $P = 0.015$). Cases received a median of 14 days (7 to 18 days) of ceftolozane-tazobactam (monotherapy in 11 cases [57.9.6%]). Ceftolozane-tazobactam was mostly used as targeted therapy (16 cases; 84.2%) because of resistance (9 cases; 47.4%), failure (4 cases; 21.1%), and toxicity (3 cases; 15.8%). Ten cases had bacteremia (52.6%). The sources were pneumonia (26.3%), catheter-related bacteremia (21.1%), primary bacteremia (21.1%), and perianal/genital (15.7%), urinary (10.5%), and skin/soft tissue (5.3%) infection. No toxicity was attributed to ceftolozane-tazobactam. More than 60% had neutropenia, and 15.8% fulfilled the criteria for sepsis. There were no significant differences in clinical cure at day 14 (89.5% versus 71.1%; $P = 0.183$) or recurrence (15.8% versus 10.5%; $P = 0.675$). Thirty-day mortality was lower among cases (5.3% versus 28.9%; $P = 0.045$). Ceftolozane-tazobactam was well tolerated and at least as effective as other alternatives for *P. aeruginosa* infection in patients with hematologic malignancy, including neutropenic patients with sepsis caused by XDR strains.

KEYWORDS ceftolozane-tazobactam, *Pseudomonas aeruginosa*, hematologic, neutropenic

Pseudomonas aeruginosa is a prevalent pathogen in patients with hematologic malignancy. Given the widespread use of broad-spectrum antibiotics in these patients, available agents that maintain activity against *P. aeruginosa* are becoming increasingly scarce, toxic, and inappropriate in terms of pharmacodynamics/pharmacokinetics.

Ceftolozane-tazobactam is a new cephalosporin with enhanced activity against *P.*

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aeruginosa. The currently approved indications are complicated intraabdominal infection and complicated urinary tract infection (1, 2).

Recent guidelines on the management of *P. aeruginosa* infection (3) allow for the use of ceftolozane-tazobactam in patients with neutropenia with <500 cells/mm^3. However, to our knowledge, no publications to date, aside from isolated case reports (4, 5), have examined its use in patients with hematologic malignancy. We present our experience in patients with hematologic malignancy and *P. aeruginosa* infection treated with ceftolozane-tazobactam as part of a compassionate use program, salvage therapy, or empirical therapy.

(This study was previously presented in part as a poster at the 28th ECCMID conference, 21 April 2018 [6]).

RESULTS

Nineteen cases and 38 controls were analyzed. Controls were treated empirically according to the hematology ward protocol (see Materials and Methods) and targeted therapy was adjusted with piperacillin-tazobactam, cefepime, ceftazidime, meropenem, ciprofloxacin, colistin, or amikacin as per *in vitro* susceptibility results.

Characteristics of cases treated with ceftolozane-tazobactam. The underlying disease was acute myeloblastic leukemia in most cases, followed by non-Hodgkin lymphoma (Table 1). Almost half of the patients had received a stem cell transplant (allogeneic or autologous). More than 60% had neutropenia with <500 cells/mm^3, and 15.8% fulfilled the criteria for sepsis according to the quick sequential organ failure assessment (qSOFA) score.

The most common presentation was bacteremia (10 of 19 cases [52.6%]). The sources were mainly pneumonia (5 cases; 26.3%), followed by catheter-related bacteremia (4 cases; 21.1%), perianal or genital infection (3 cases; 15.7%), urinary infection (2 cases; 10.5%), and skin/soft tissue infection (1 case; 5.3%). Four cases presented with primary bacteremia (21.1%).

Ceftolozane-tazobactam was used mostly as targeted therapy (16 cases; 84.2%) for resistance (9 cases; 47.4%), failure (4 cases; 21.1%), or toxicity of previous antibiotics (3 cases; 15.8%). The drug was used empirically in 3 cases (15.8%) because of suspicion of resistance to other antimicrobials. All cases had been treated with other antibiotics before ceftolozane-tazobactam except 2, and as many as 7 had previously received more than 1 line of antibiotics. Ceftolozane-tazobactam was started a median of 2 days after the diagnosis of the *P. aeruginosa* infection.

Cases received a median of 9.5 prescribed daily doses (PDD) of ceftolozane-tazobactam (interquartile range, 6 to 15) over a median of 14 (range, 7 to 18) days (11 as monotherapy; 52.6%). Eight cases received ceftolozane-tazobactam combined with other antibiotics for a median of 14 (range, 3.5 to 17.5) days. The antibiotics used in combination therapy with ceftolozane-tazobactam were amikacin plus levofloxacin (2 cases), amikacin (4 cases), colistin (1 case), or fosfomycin (1 case).

A dose of 2 g/1 g every 8 h (q8h; or an equivalent dose adjusted for renal function) was used for pneumonia and bloodstream infection. The median MIC for ceftolozane-tazobactam was 2 mg/liter (range, 1.5 to 3 mg/liter). None of the isolates was resistant to ceftolozane-tazobactam (MIC ≤4 mg/liter), and none of them was found to be a carbapenemase producer.

Differences between cases and controls. Cases were younger (45.6 years versus 57.6 years; $P = 0.012$) and less often had bacteremia (52.6% versus 86.8%; $P = 0.008$), although they did have a worse Multinational Association for Supportive Care in Cancer (MASCC) score (10.2 versus 16.1; $P = 0.0001$). They also had more hospital-acquired infections than controls (78.9% versus 47.4%, respectively; $P = 0.013$) and more frequently were infected with extremely drug-resistant (XDR) *P. aeruginosa* (47.4% versus 21.1%, respectively; $P = 0.015$). There were no significant differences between cases and controls regarding underlying hematologic malignancy, stage, source of infection, need for admission to the intensive care unit (ICU), prevalence of sequence type 175 (ST175) clone, appropriateness of empirical therapy, or neutropenia.

TABLE 1 Characteristics of cases treated with ceftolozane-tazobactam and controls

Characteristic[a]	Total	Cases	Controls	*P* value
No. of cases	57	19	38	
Male (*n* [%])	43	16 (84.2)	27 (71.1)	0.343
Age (years) (mean [SD])	53.6 (17.2)	45.6 (14.6)	57.6 (17.2)	0.012
Hematologic malignancy (*n* [%])				0.125
AML	17 (29.8)	10 (52.6)	7 (18.4)	
ALL	8 (14)	2 (10.5)	6 (15.8)	
NHL	17 (29.8)	5 (26.3)	12 (31.6)	
HL	1 (1.8)	0 (0)	1 (2.6)	
MDS	5 (8.8)	0 (0)	5 (13.2)	
MM	5 (8.8)	0 (0)	5 (13.2)	
AA	1 (1.8)	1 (5.3)	1 (2.6)	
Other	1 (1.8)	1 (5.3)	1 (2.6)	
Stage (*n* [%])				0.118
Induction	11 (19.3)	3 (15.8)	8 (21.1)	
Consolidation	10 (17.5)	6 (31.6)	4 (10.5)	
Reinduction	12 (21.1)	5 (26.3)	7 (18.4)	
Allo-HSCT	14 (24.6)	5 (26.3)	9 (23.7)	
Auto-HSCT	5 (8.8)	0 (0.0)	5 (13.2)	
Progression	5 (8.8)	0 (0)	5 (13.2)	
MASCC score (mean [SD])	14.1 (6.2)	10.2 (2.7)	16.1 (6.6)	0.0001
MASCC score <21 (*n* [%])	42 (75.0)	19 (100.0)	23 (62.2)	0.002
Charlson (mean [SD])	3.18 (2.1)	3 (1.96)	3.26 (2.20)	0.659
Age-adjusted Charlson (mean [SD])	4.26 (2.63)	3.63 (2.14)	4.58 (2.83)	0.204
Comorbidities(*n* [%])				0.461
Liver disease	1 (1.8)	0 (0.0)	1 (2.6)	
COPD	7 (12.3)	0 (0.0)	7 (18.4)	
Heart disease	6 (10.5)	3 (15.8)	3 (7.9)	
HIV	2 (3.5)	1 (5.3)	1 (2.6)	
Diabetes	4 (7.0)	2 (10.5)	2 (5.3)	
CKD	3 (5.3)	1 (5.3)	2 (5.3)	
Other	6 (10.5)	1 (5.3)	5 (13.2)	
Place of acquisition (*n* [%])				0.013
Hospital acquired	33 (57.9)	15 (78.9)	18 (47.4)	
Healthcare associated	11 (19.3)	4 (21.1)	7 (18.4)	
Community acquired	13 (34.2)	0 (0.0)	13 (34.2)	
Source of infection (*n* [%])				0.738
CVC/PICC	12 (21.1)	4 (21.1)	8 (21.1)	
Respiratory	14 (24.6)	5 (26.3)	9 (23.7)	
Urinary	12 (21.1)	2 (10.5)	10 (26.3)	
Skin and soft tissue	4 (7.0)	1 (5.3)	3 (7.9)	
Genital	5 (8.8)	2 (10.5)	3 (7.9)	
Perianal	3 (5.3)	1 (5.3)	3 (5.3)	
Primary	7 (12.3)	4 (21.1)	3 (7.9)	
Length of stay prior to infection (days) (mean [SD])	23.6 (34.9)	30.4 (39.4)	20.2 (32.6)	0.302
Leucocytes (cells/mm^3) (mean [SD])	3,219 (7,617)	3,478 (10,511)	3,089 (5,831)	
Neutropenia <500 cells/mm^3 (*n* [%])	32 (56.1)	12 (63.2)	20 (52.6)	0.574
Duration of neutropenia prior to infection (days) (mean [SD])	19.8 (37.7)	24.9 (45.3)	17 (33.5)	0.540
New renal failure (*n* [%])	16 (31.4)	7 (41.2)	9 (26.5)	0.345
SOFA (mean [SD])	4.84 (3.57)	5.42 (3.0)	4.5 (3.9)	0.379
Sepsis according to qSOFA (*n* [%])	10 (17.9)	3 (15.8)	7 (18.9)	NS[b]
ICU admission (*n* [%])	12 (21.1)	5 (26.3)	7 (18.4)	0.509
Bloodstream infections (*n* [%])	43 (75.4)	10 (52.7)	33 (86.8)	0.008
Pitt bacteremia score (mean [SD])	1.39 (1.8)	1.21 (1.3)	1.46 (1.9)	0.672
Susceptibility (no. [%] of nonsusceptible strains)				
Piperacillin-tazobactam	29 (50.9)	18 (94.7)	11 (29.0)	0.0001
Ceftazidime	31 (54.4)	16 (84.2)	15 (39.5)	0.0001
Cefepime	38 (66.7)	18 (94.7)	18 (47.4)	0.0001
Aztreonam	49 (87.5)	18 (94.7)	31 (83.7)	0.426

(Continued on next page)

TABLE 1 (Continued)

Characteristic[a]	Total	Cases	Controls	*P* value
Imipenem	42 (76.4)	19 (100)	25 (65.8)	0.015
Meropenem	42 (77.8)	19 (100)	23 (65.7)	0.028
Gentamicin	46 (80.7)	19 (100)	27 (71.1)	0.009
Tobramycin	46 (80.7)	19 (100)	27 (71.1)	0.009
Amikacin	7 (12.5)	2 (10.6)	5 (13.5)	0.349
Fosfomycin	20 (40.0)	8 (42.1)	12 (38.7)	0.308
Ciprofloxacin	45 (80.4)	19 (100)	25 (67.6)	0.015
Colistin	0/43 (0)	0 (0)	0 (0)	0.828
Ceftolozane-tazobactam	0/19 (0)	0 (0)	0 (0)	NS
Resistance (CDC) (*n* [%])				0.015
Non-multidrug resistant	11 (19.3)	0 (0.0)	11 (28.9)	
MDR	29 (50.9)	10 (52.6)	9 (50.0)	
XDR	17 (29.8)	9 (47.4)	8 (21.1)	
ST175 clone	25 (83.3)	11 (100)	14 (73.7)	0.129
Appropriate empirical treatment (*n* [%])	28 (49.1)	8 (42.1)	20 (52.6)	0.576
Combined therapy (*n* [%])	20 (35.1)	8 (42.1)	12 (31.6)	0.558
Source control (*n* [%]) or (no./total no.)	14/19	5 (71.4)	9 (75.0)	NS
Toxicity (*n* [%])	10 (17.5)	5 (26.3)[c]	5 (13.2)	0.119
Clinical cure (*n* [%]) or (no./total no.)				
14 days	44 (77.2)	17 (89.5)	27 (71.1)	0.183
Monotherapy	31/37	10 (90.9)	21 (80.8)	0.646
Combined therapy	13/20	7 (87.5)	6 (50.0)	0.158
Recurrence (*n* [%]) or (no./total no.)	7 (12.3)	3 (15.8)	4 (10.5)	0.675
Monotherapy	4/37	1 (10)	3 (11.5)	NS
Combined therapy	3/20	2 (22.2)	1 (8.3)	0.537
30-day mortality (*n* [%]) or (no./total no.)	12 (5.3)	1 (5.3)	11 (28.9)	0.045
Monotherapy	6/37	1 (10)	5 (19.2)	NS
Combined therapy	6/20	0 (0)	6 (50.0)	0.042
Time from infection to death (days) (mean [SD])	157.3 (296.7)	41.7 (30.1)	175.6 (316.3)	0.481

[a]AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; AA, aplastic anemia; HSCT, hematopoietic stem cell transplant; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVC, central venous catheter; PICC, peripherally inserted central catheter; SOFA, sequential organ failure assessment; ICU, intensive care unit; MDR, multidrug resistant; XDR, extremely drug resistant; SD, standard deviation.

[b]NS, not significant.

[c]Toxicity attributable to empirical therapy administered before ceftolozane-tazobactam or to other drugs administered with ceftolozane-tazobactam as combined therapy.

Outcomes. (i) Safety. No toxicity was attributable to ceftolozane-tazobactam. Antibiotic toxicity (nephro- or neurotoxicity) was detected in 13.2% of controls. Nephrotoxicity was detected in 26.3% of cases and was attributed to other antibiotics used prior to or concomitantly with ceftolozane-tazobactam.

(ii) Efficacy. There were no significant differences in clinical cure at day 14 (89.5% versus 71.1%; $P = 0.183$) or in recurrence (15.8% versus 10.5%; $P = 0.675$). However, 30-day mortality was significantly lower among cases than controls (5.3% versus 28.9%, respectively; $P = 0.045$) in the univariate and multivariate analyses (Table 2). Interestingly, there were no deaths in cases treated with combination therapy but there were for the controls also treated with combination therapy not including ceftolozane-tazobactam (0% versus 50%, respectively; $P = 0.042$).

TABLE 2 Multivariate analysis of cases and controls

Variable	OR	95% CI	*P* value
Age	0.910	0.835–0.992	0.033
MASCC score	0.583	0.388–0.876	0.009
30-day mortality rate	0.008	0.0001–0.298	0.009

Subset of patients with bacteremia. Among the factors that differed between cases and controls, only bacteremia was associated with clinical cure at day 14 (69.8% versus 100%; $P = 0.025$) or 30-day mortality (27.9% versus 0%; $P = 0.027$) in the univariate analysis. To address this issue, bacteremic episodes were compared separately (Table 3). The association disappeared when ceftolozane-tazobactam was introduced in the multivariate model.

Ten cases were compared with 33 controls (Table 3). Patients with bacteremia treated with ceftolozane-tazobactam had higher partial pressures of oxygen (pO_2; mean, 100 mm Hg [0] versus 73.7 mm Hg [30.8]; $P = 0.018$) but worse MASCC scores (mean [standard deviation], 10.2 [2.8] versus 16.5 [6.7]; $P = 0.0001$) and lower leukocyte counts (mean [standard deviation], 320 [545.2] cells/mm^3 versus 3,024 [6,193.6] cells/mm^3; $P = 0.018$). There was a nonsignificant trend toward a higher proportion with clinical cure and a lower 30-day mortality.

Subset of patients with multidrug-resistant strains. Multidrug resistance was more frequent among cases than controls, but was not associated with mortality. Episodes of *P. aeruginosa* infection caused by XDR strains had a 29.4% (38.5% for bacteremic episodes) mortality compared to 13.8% (bacteremic episodes,18.2%) for MDR strains and 27.3% (bacteremic episodes, 37.5%) for non-multidrug-resistant strains. Drug resistance was not significantly associated with mortality.

Multilocus sequence typing (MLST) to detect ST175 was only available for 30 strains, both MDR and XDR. Even though XDR strains were more frequent among cases, there was no significant difference between cases and controls in the distribution of the ST175 clone (100% versus 73.7%, respectively; $P = 0.129$) (Table 4).

We analyzed separately the episodes with XDR strains. There was a trend toward a higher clinical cure at day 14 among patients treated with ceftolozane-tazobactam compared to that among controls, both in the general group (88.9% versus 37.5%, respectively; $P = 0.050$) and in bacteremic episodes (80.0% versus 37.5%, respectively; $P = 0.266$). As well, there was a trend toward a lower 30-day mortality in episodes treated with ceftolozane-tazobactam (general group, 11.1% versus 50.0%, $P = 0.131$; bacteremic episodes, 20% versus 50%, $P = 0.565$).

DISCUSSION

The present study shows that ceftolozane-tazobactam was well tolerated and at least as effective as other therapeutic alternatives for *P. aeruginosa* infection in patients with hematologic malignancy, including neutropenic patients with sepsis caused by XDR strains.

P. aeruginosa infections are common and particularly severe in patients with hematologic malignancy (7). The generalized use of broad-spectrum antimicrobials in neutropenic patients is leading to the selection of more resistant strains of *P. aeruginosa*. The few antibiotic options left to treat them are toxic and only moderately successful (3, 8). In the absence of carbapenemases, resistance to imipenem and meropenem is driven by porin OprD2 (imipenem) and efflux pump OprM (meropenem). None of these affect ceftolozane-tazobactam, which is also stable against the chromosomal cephalosporinase AmpC, and this context of carbapenem resistance represents, as a matter of fact, the circumstances in which ceftolozane-tazobactam would be indicated. Ceftolozane-tazobactam is thus a promising new option, although data from patients with hematologic malignancy are lacking. In addition, while real-life experiences of ceftolozane-tazobactam have been published, data on its use in hematologic malignancy remain rare (4, 5, 9–11). Hakki and Lewis (12) reported a clinical success rate of 83.3% in multidrug-resistant *P. aeruginosa* infections treated with ceftolozane-tazobactam in 6 patients with hematologic malignancy. The authors did not make a comparison with cases not treated with ceftolozane-tazobactam. In the present study, we report a clinical success rate of 89.5% and a significantly reduced 30-day mortality compared with that in controls. The use of high doses of ceftolozane-tazobactam and combination therapy in 47.4% of patients may have contributed to this success.

TABLE 3 Characteristics of patients with bacteremia treated with ceftolozane-tazobactam and controls

Variable[a]	Total	Cases	Controls	*P* value
No. of cases	43	10	33	
Male (*n* [%])	32	8 (80)	24 (72.7)	NS[b]
Age (years) (mean [SD])	55.2 (16.1)	50.3 (12.8)	56.7 (16.8)	0.275
Hematologic malignancy (*n* [%])				0.05
AML	14 (32.6)	7 (70)	7 (21.2)	
ALL	4 (9.3)	0 (0)	4 (12.1)	
NHL	12 (27.9)	2 (20)	10 (30.3)	
HL	1 (2.3)	0 (0)	1 (3)	
MDS	5 (11.6)	0 (0)	5 (15.2)	
MM	5 (11.6)	0 (0)	5 (15.2)	
AA	1 (2.3)	0 (0)	1 (3)	
Other	1 (2.3)	1 (10)	0 (0)	
Stage (*n* [%])				0.03
Induction	8 (18.6)	0 (0)	8 (24.2)	
Consolidation	6 (14)	2 (20)	4 (12.1)	
Reinduction	8 (18.6)	5 (50)	3 (9.1)	
Allo-HSCT	12 (27.9)	3 (30)	9 (27.3)	
Auto-HSCT	4 (9.3)	0 (0)	4 (12.1)	
Progression	5 (11.6)	0 (0)	5 (15.2)	
MASCC score (mean [SD])	15 (6.5)	10.2 (2.8)	16.5 (6.7)	0.0001
MASCC score <21 (*n* [%])	29 (69)	10 (100)	19.8 (59.4)	0.018
Charlson (mean [SD])	3.1 (2.1)	3.3 (2.5)	3.1 (1.9)	0.756
Age-adjusted Charlson (mean [SD])	4.2 (2.7)	3.9 (2.5)	4.3 (2.8)	0.709
Comorbidities (*n* [%])				0.716
Liver disease	1 (2.3)	0 (0)	1 (3.0)	
COPD	6 (14.0)	0 (0)	6 (18.2)	
Heart disease	3 (7.0)	1 (10.0)	2 (6.1)	
HIV	2 (4.7)	1 (10.0)	1 (3.0)	
Diabetes	3 (7.0)	1 (10.0)	2 (6.1)	
CKD	3 (7.0)	1 (10.0)	2 (6.1)	
Other	3 (7.0)	0 (0)	3 (17.6)	
Place of acquisition (*n* [%])				0.078
Hospital acquired	24 (55.8)	8 (80)	16 (48.5)	
Healthcare associated	7 (16.3)	2 (20)	5 (15.2)	
Community acquired	12 (27.9)	0 (0)	12 (36.4)	
Infection source (*n* [%])				0.544
CVC/PICC	11 (25.6)	3 (30)	8 (24.2)	
Respiratory	8 (18.6)	2 (20)	6 (18.2)	
Urinary	10 (23.3)	2 (20)	8 (24.2)	
Skin and soft tissue	3 (7)	0 (0)	3 (9.1)	
Genital	3 (7)	0 (0)	3 (9.1)	
Perianal	2 (4.79	0 (0)	2 (6.1)	
Primary	6 (14)	3 (30)	3 (9.1)	
Length of stay prior to infection (days) (mean [SD])	23.7 (37.7)	34.8 (51.3)	20.4 (32.9)	0.296
Leucocytes (cells/mm^3) (mean [SD])	2,395 (5,534)	320 (545.3)	3,024 (6,193.6)	0.018
Neutropenia (*n* [%])	27 (62.8)	8 (80)	19 (57.6%)	0.276
Neutropenia duration prior to infection (days) (mean [SD])	22.8 (41.3)	36.3 (56.9)	18.1 (34.7)	0.419
Platelets (mean no. [SD])	42,116 (67830)	18,300 (11284)	49,333 (75973)	0.030
New renal failure (*n* [%])	12 (30.8)	4 (40)	8 (26.7)	0.416
pO_2 (mm Hg) (mean [SD])	79.4 (29.2)	100	73	0.018
Respiratory rate at presentation (breaths/min) (mean [SD])	22 (6.2)	15	24	0.0001
qSOFA criteria (mean no. [SD])	0.71 (0.9)	0.6 (0.7)	0.75 (0.95)	0.648
Sepsis according to qSOFA (*n* [%])	8 (19)	1 (10)	7 (21.9)	0.655
SOFA (mean [SD])	5.2 (3.8)	6.4 (2.9)	4.74 (4.1)	0.246
ICU required (*n* [%])	9 (20.9)	2 (20)	7 (21.2)	NS
Pitt bacteremia score (mean [SD])	1.5 (1.8)	1.3 (1.4)	1.5 (1.9)	0.719
Susceptibility (no. [%] of nonsusceptible strains)				
Piperacillin-tazobactam	19 (44.2)	9 (90)	10 (30.4)	0.0001

(Continued on next page)

TABLE 3 (Continued)

Variable[a]	Total	Cases	Controls	*P* value
Ceftazidime	22 (51.2)	8 (80)	14 (42.4)	0.005
Cefepime	28 (65)	9 (90)	19 (57.6)	0.002
Aztreonam	36 (83.7)	9 (90)	27 (81.8)	0.411
Imipenem	33 (76.7)	10 (100)	23 (69.7)	0.110
Meropenem	32 (78.0)	10 (100)	22 (71.0)	0.298
Gentamicin	35 (81.4)	10 (100)	25 (75.8)	0.084
Tobramycin	35 (81.4)	10 (100)	25 (75.8)	0.084
Amikacin	6 (14)	1 (10)	5 (15.2)	0.680
Fosfomycin	17 (48.6)	5 (50)	12 (48.0)	0.542
Ciprofloxacin	33 (76.7)	10 (100)	23 (69.7)	0.047
Colistin	0 (0)	0 (0)	0 (0)	0.332
Ceftolozane-tazobactam	0 (0)	0 (0)	0 (0)	NS
Resistance (CDC) (*n* [%])				0.128
Non-multidrug resistant	8 (18.6)	0 (0)	8 (24.2)	
MDR	22 (51.2)	5 (50)	17 (51.5)	
XDR	13 (30.2)	5 (50)	8 (24.2)	
ST175 clone	21 (80.2)	8 (100)	13 (72.2)	0.281
Appropriate empirical treatment (*n* [%])	22 (51.2)	6 (60)	16 (48.5)	0.721
Combined therapy (*n* [%])	18 (41.9)	12 (36.4)	6 (60)	0.275
Source control (*n* [%]) or (no./total no. [%])	11/16 (68.8)	3 (60)	8 (72.7)	NS
Toxicity (*n* [%])	9 (20.9)	4 (40)[c]	5 (15.2)	0.143
Clinical cure (*n* [%])				
14 days	30 (69.8)	8(80.0)	22 (66.7)	0.696
Monotherapy	19 (76)	3 (75)	16 (76.2)	NS
Combined therapy	11 (61.1)	5 (83.3)	6 (50)	0.316
Recurrence (*n* [%]) or (no./total no. [%])	4 (9.3)	2 (20.0)	2 (6.1)	0.226
Monotherapy	1/25 (4.0)	0 (0)	1 (4.8)	NS
Combined therapy	3/18 (16.7)	2 (33.3)	1 (8.3)	0.245
30-day mortality (*n* [%]) or (no./total no. [%])	12 (27.9)	1 (10)	11 (33.3)	0.237
Monotherapy	6/25 (24)	1 (25)	5 (23.8)	NS
Combined therapy	6/18 (33.3)	0 (0)	6 (50)	0.054
Time from infection to death (days) (mean [SD])	157.3 (296.8)	41.7 (30.0)	175.6 (316.3)	0.481

[a]AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; AA, aplastic anemia; HSCT, hematopoietic stem cell transplant; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVC, central venous catheter; PICC, peripherally inserted central catheter; SOFA, sequential organ failure assessment; ICU, intensive care unit; MDR, multidrug resistant; XDR, extremely drug resistant; SD, standard deviation.

[b]NS, not significant.

[c]Toxicity attributable to empirical therapy administered before ceftolozane-tazobactam or to other drugs administered with ceftolozane-tazobactam as combined therapy.

Importantly, no deaths were detected among episodes treated with combination therapy including ceftolozane-tazobactam.

Three cases presented recurrent *P. aeruginosa* infections. Recurrence was related to infected catheters that were left in place in at least 2 cases.

The development of resistance to ceftolozane-tazobactam is a matter of concern (9,

TABLE 4 Distribution of ST175 clone in 30 episodes

		No. (%) of cases		
Resistance	ST175	Cases (*n* = 11)	Controls (*n* = 19)	Total (*n* = 30)
Non-multidrug resistant	No	0 (0)	3 (75)	3 (75)
	Yes	0 (0)	1 (25)	1 (25)
MDR	No	0 (0)	2 (22.2)	2 (13.3)
	Yes	6 (100)	7 (77.8)	13 (86.7)
XDR	No	0 (0)	0 (0)	0 (0)
	Yes	5 (100)	6 (100)	11 (100)

13, 14). Hakki and Lewis (12) describe a ceftolozane–tazobactam-resistant strain in a case of recurrent hematologic malignancy that had been treated with ceftolozane-tazobactam monotherapy. In our series, no resistance to ceftolozane-tazobactam was detected in recurrent cases. Two recurrent cases had been treated with combination therapy, although one of them only received the combination for 24 h. It remains unclear whether combination therapy might be a protective factor against the development of resistance.

Similar to other series (12), we did not detect toxicity attributable to ceftolozane-tazobactam, whereas alternative agents induced nephrotoxicity and neurotoxicity. Of note, when combination therapy was administered, nephrotoxicity was also reported. In some cases, the reason for choosing ceftolozane-tazobactam was the previous toxicity of alternative therapies, and this factor may account for the higher nonattributable toxicity among cases in the study group.

Our study is subject to limitations. First, it is a small single-center study, and our results need to be confirmed in other settings. Second, as the study was not a clinical trial, cases and controls were not balanced in terms of bloodstream infections, thus favoring cases, or in terms of *P. aeruginosa* resistance profiles and MASCC scores, thus favoring controls. Only bacteremia was associated with clinical cure at day 14 or 30-day mortality among factors that differed between cases and controls, and that association disappeared when introducing ceftolozane-tazobactam in the multivariate model. When analyzed separately, the results of bacteremic episodes were in line with those of the general study. Median ages also differed between cases and controls but were not associated with mortality in this study.

Multidrug-resistant strains were more frequent among the cases. It has been documented that XDR strains show a lower virulence, particularly ST175, which is the XDR clone most frequent in Spain (15). But the association between XDR and mortality is not straight forward, as inappropriate therapy is more common for XDR strains. In the present series, with an overall prevalence of multidrug-resistant strains of 80.7%, the ST175 clone was equally distributed between cases and controls, and mortality did not differ significantly depending on resistance. A recent study from the same country (16) also reported a high incidence of multidrug-resistant *P. aeruginosa* treated with ceftolozane-tazobactam, with a clinical success of 63.8%. The increased risk of clinical failure in XDR strains was not significant in that series, and the high proportion of critically ill patients may account for the lower success rate than ours.

Ceftolozane-tazobactam was well tolerated and had an almost 90% clinical success rate in multidrug-resistant *P. aeruginosa* infections in high-risk patients with hematologic malignancy. A comparison with alternative therapies revealed a decrease in 30-day mortality. Our real-life experience should be considered proof of concept for the use of ceftolozane-tazobactam in high-risk patients with hematologic malignancy. The most appropriate dose of ceftolozane-tazobactam for bloodstream infection and the need for combination therapy have yet to be defined. These promising results need to be confirmed by further studies in larger populations and support the need to establish a clinical trial to determine whether ceftolozane-tazobactam provides a benefit in *P. aeruginosa* infections in patients with hematologic malignancy.

MATERIALS AND METHODS

Ethics. The study and the case report form were approved by the local institutional review board and ethics committee (MICRO.HGUGM.2018-002).

Setting. Our institution is a 1,250-bed tertiary teaching hospital in Madrid, Spain. During the study period, its catchment population was 350,000 inhabitants. The hematology department consists of a hematopoietic stem cell transplantation unit with 8 beds and a hematological ward with 13 beds. An infectious diseases physician works together with the hematology team in all cases of bloodstream infection and in infections due to multidrug-resistant microorganisms. Ceftolozane-tazobactam has been available for use in our hospital since March 2016.

Patients. We performed a single-center case-control study including all patients with hematologic malignancy and *P. aeruginosa* infection treated with ceftolozane-tazobactam (study group) from March 2016 to February 2018 and compared them with patients with hematologic malignancy and *P. aeruginosa* infection not treated with ceftolozane-tazobactam (control group, 2 controls per case) to assess safety and effectiveness.

A protocol including clinical and microbiologic data for each episode was completed.

Clinical criteria and definitions. Cases were patients with hematologic malignancy and infection and a positive *P. aeruginosa* culture who had received at least 48 h of ceftolozane-tazobactam. Controls were patients with hematologic malignancy and infection and a positive culture for *P. aeruginosa* who had not received ceftolozane-tazobactam.

Conventional criteria (17, 18) were used to determine the place of acquisition. Community-acquired infection was defined as that diagnosed within the first 48 h of admission. After this period, the infection was considered hospital acquired. Health care-associated infection was diagnosed within 48 h of the admission of an outpatient with any of the following criteria (19): intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of infection; attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of infection; hospitalization in an acute care hospital for $\geq$2 days during the 90 days before the onset of infection; or residence in a nursing home or long-term-care facility.

We used the age-adjusted Charlson comorbidity index to categorize comorbidities (20). Infection was classified according to clinical and microbiologic criteria according to the Centers for Disease Control guidelines (18). qSOFA was defined according to the third international consensus definitions for sepsis and septic shock (21). Acute renal failure was defined as a 2-fold increase in the serum creatinine value in patients with previous normal renal function or an increase of 50% in the baseline creatinine level in patients with preexisting renal dysfunction, according to the RIFLE criteria (22). Neutropenia was defined as an absolute neutrophil count of $<$500 cells/mm^3 (23).The MASCC (Multinational Association for Supportive Care in Cancer) score to identify risk of febrile neutropenia complications was calculated according to Klastersky et al. (24). Bacteria were classified as multidrug-resistant microorganisms according to the criteria described by Magiorakos et al. (25).

We considered antibiotic therapy to be empirical when it was administered before susceptibility results were available and to be targeted when it was administered after susceptibility results were available. During the study period, the empirical therapy for sepsis in the hematology ward was piperacillin-tazobactam. It was substituted for meropenem in patients known to be colonized by extended-spectrum β-lactamase (ESBL)-producing organisms. Glycopeptide and amikacin were added if necessary. Levofloxacin prophylaxis was administered to patients with expected prolonged neutropenia. The prescribed daily dose (PDD) of antibiotics was measured according to de With et al. (26). We considered the initial treatment with an effective antibiotic according to *in vitro* susceptibility testing as appropriate empirical therapy (27). Thirty-day mortality was evaluated.

Laboratory procedures. Bacteria were identified by using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (28), and susceptibility testing of isolates was performed using commercialized microdilution MicroScan panels (Beckman Coulter, West Sacramento, CA, USA). Susceptibility tests were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations (29).

The ceftolozane-tazobactam MIC was determined using the gradient diffusion method (MICtest strip; Liofilchem, Italy) in cation-adjusted Mueller-Hinton agar. The Xpert Carba-R PCR (Cepheid, Sunnyvale, CA) was used for carbapenemase detection.

Multilocus sequence typing was performed in the context of a different study that will be published elsewhere and was available only for 30 strains. The MLST types of the strains were obtained by uploading the fastq sequences to the online tool MLST 2.0 (Center of Genomic Epidemiology) (30).

Data analysis. Cases treated with ceftolozane-tazobactam were compared with controls not treated with ceftolozane-tazobactam in terms of baseline characteristics (clinical presentation and pattern of resistance of *P. aeruginosa*), safety (tolerance and adverse effects), and effectiveness (clinical and microbiological cure, outcome, recurrences, complications, and mortality).

Quantitative variables are expressed as means (standard deviations) or medians (interquartile ranges), as appropriate; qualitative variables are expressed as frequencies and percentages. Continuous variables were compared using the *t* test, and categorical variables were compared using the χ^2 test or Fisher exact test when the χ^2 test was not appropriate.

Adjusted odds ratios (ORs) were computed using logistic regression analysis to compare cases and controls. Stepwise logistic regression analysis was performed including variables with a *P* value of $<$0.1 in the univariate analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

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