UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

Faculdade de Farmácia

Trabalho de Conclusão de Curso de Farmácia

Tigecycline: the use in an universitary hospital may lead to better outcomes?

Bianca Rocha da Silva

Porto Alegre, Dezembro de 2018

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Trabalho de Conclusão de Curso apresentado como requisito parcial para obtenção do grau de farmacêutica pelo curso de Farmácia da Universidade Federal do Rio Grande do Sul.

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*"*Sejam quais foram os resultados, com êxito ou não, o importante é que no final cada um possa dizer: fiz o que pude."

(Louis Pasteur)

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STATEMENT OF DECLARATION OF INTEREST

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Tigecycline: the use in an universitary hospital may lead to better outcomes?

Running title: High doses of tigecycline: better outcomes?

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Abbreviations:

TGC = tigecycline, FDA = Food and Drug Administration, EMA = European Medicines Agency, WHO = World Heath Organization, ANVISA = Agência Nacional de Vigilância Sanitária, HCPA = Hospital de Clínicas de Porto Alegre, ICU = Intensive Care Unit, MIC = Minimum Inhibitoy Concentration, EUCAST = European Committe on Antimicrobial Susceptibility; APACHE II = Acute Physiology and Chronic Health Evaluation II, SAPS III = Simplified Acute Physiology III

Abstract

Objectives: The aim of this study was to asses the use of tigecycline in differents therapeutic schemes in an universitary hospital.

Methods: A retrospective study was conducted, including data (prontuary review) of patients who used tigecycline at a tertiary teaching hospital from January/2015 to March/2018. Patients were divided into two groups: group "standard dose", with patients using 100 mg as attack dose, followed by 50 mg of tigecycline every 12 hours; and group "high dose", including patients who used 200 mg, followed by 100 mg every 12 hours.

Results: 43 patients received high doses and 44, standard doses of tigecycline. The main etiological agents were *Klebsiella pneumoniae* (87%), which were recovered from different body sites. Overall in-hospital mortality was 55.2%, with no significant difference between groups ($p > 0.05$). Also, there was no difference between survival time ($p > 0.05$).

Conclusion: Among patients enrolled in this study, there was no statistically significant difference in mortality between the two groups. Heterogeneity of types of infections is our major limitation. More studies are necessary to definitively elucidate influence of high dose's based schemes in each particular type of infections.

Keywords: tigecycline; multidrug resistant bacteria; high dose

1. Introduction

Because bacterial resistance to antimicrobials is a global and emerging public health problem, the search for new therapeutical options is a subject of major concern (WHO, 2014) especially considering gram-negative bacilli resistant to carbapenems (WHO, 2018). Tigecycline (TGC), a glycylglycine derived from tetracyclines, is one of the few alternatives available for the treatment of infections caused by these pathogens, showing good *in vitro* activity against many multiresistant microorganisms (Cercenado *et al*., 2003; Goldstein *et al*. 2006; Souli *et al*., 2006).

TGC was approved by the US Food and Drug Administration (FDA) in 2005 and by the European Medicines Agency (EMA) in 2006. The drug was approved for the treatment of complicated skin and soft-tissue infections, as well as complicated intra-abdominal infections, at the loading dose of 100 mg, followed by 50 mg every 12 hours, intravenously, for 5 to 14 days and 7 to 14 days, respectively (Babinchack *et al*., 2005; Ellis-Grosse *et al*., 2005). In 2009, it was also approved for use in community-acquired pneumonia (Bergallo *et al*., 2009; Dartois *et al*., 2008). In Brazil, it was licensed in 2014 (Anvisa, 2018). In addition, this antimicrobial has often been used in off-label indications, such as in bloodstream infections or nosocomial pneumonias caused by carbapenem-resistant Gram-negative bacilli (Babinchack and Stein, 2013; Moghnieh *et al*., 2017).

In 2010, the FDA added a box warning on the label (FDA 2010 and 2013), due to results of meta-analysis concluding that there is an association of TGC and excess deaths, even when used in approved indications (Prasad *et al*., 2012). Those studies also highlighted that TGC is no better option than other available antibiotics (Shen *et al*., 2015; Tasina *et al*., 2011). Indeed, the association with other drugs (aminoglycosides, carbapenems, polymyxins, for example) has proved to be more effective than monotherapy (Tumbarello *et al*., 2012; Zarkotou *et al*., 2011).

Population pharmacokinetic studies evidenced a lower concentration of TGC in some body sites, such as lung and bloodstream, justifying the use of higher doses and combined therapy in clinical practice (Giamarellou and Poulakou, 2011). In addition, such studies indicated that in critical patients with higher body mass indexes, high doses are required to eradicate Gram-negative bacilli infections (Xie *et al*., 2017). Indeed, there is growing

evidences that the use of high doses may be related to better clinical outcomes (Geng *et al*., 2018), but there are still limited clinical studies on this issue.

The drug has been used in the Hospital de Clínicas de Porto Alegre (HCPA) since 2014, in sporadic situations. In 2017, it has been included in the List of Selected Medications with Restricted Dispensation, i.e., requiring justification by the prescriber, which is evaluation by the Medication and Therapeutics Committee's executive doctors for approval, due to the possibility of selection of resistant microorganisms and their high cost (approximately, USD 45,00/bottle). The situation in which the use of tigecycline in the Hospital is standardized is for the treatment of infections caused by multiresistant germs, such as carbapenem-resistant *Klebsiella pneumoniae* and panresistant *Acinetobacter baumannii*. In 2017, the cumulative incidence rate (infection and colonization) of carbapenem-resistant enterobacteria in HCPA was 1.4 (n = 355) and 0.3 (n = 89) of carbapenem-resistant *Acinetobacter baumannii*. Because frequently the drug has being used empirically and in high doses for severe patients, the objective of this study was to evaluate the clinical and microbiological outcomes of patients using tigecycline, in different therapeutic regimens in this hospital environment.

2. Materials and methods

2.1 Study desing and population: This study was an observational and retrospective serie of cases. It was performed at the Hospital de Clínicas de Porto Alegre, a public tertiary teaching hospital, with 842 beds, 87 of them from Intensive Care Units (ICUs). In 2017, there were about 30,000 hospitalizations and 3,200,000 exams performed (Institutional HCPA, 2018). Sampling was by convenience and constituted by all patients who used TGC from January 1, 2015 to March 31, 2018, totaling 86 individuals, including 15 patients under 18 years old.

In those patients in whom TGC was used more than once in the same hospitalization, the variables referring exclusively to the first use of the drug were considered. When this antimicrobial was used by the same patient in different hospitalizations, with an interval of 15 days or more, the first use in each hospitalization periods was considered. Four patients fit into this situation, totaling 90 clinical uses of TGC. Among them, the lack of data on antimicrobial use during hospitalization was an exclusion criterion, eliminating 3 patients. Therefore, 87 clinical situations where TGC was used were evaluated.

2.2 Ethics considerations: The present study was approved and registered in the HCPA Research Ethics Committee (number 150592). It was carried out considering all the ethical aspects related to human research, guaranteeing the confidentiality of all data collected. There was no need for an Informed Consent Term, given the retrospective nature of the study.

2.3 Definitions: Severe neutropenia was defined as an absolute neutrophil count less than or equal to $0.5x10^9$/L in the blood (Dale *et al*., 2016). Bacteremia was defined as one or more positive blood culture. If more than one positive culture was obtained from any patient, the bacteria recovered most closely to the onset of TGC use was considered. The same was applied for cultures of others sites of infection. Empirical use of TGC was defined as administration of the drug without an isolated etiologic agent in culture prior to initiation of treatment. Minimum Inhibitory Concentrations (MIC) for TGC was interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST): MIC < 2 μg/mL were considered susceptible, MIC = 2 μg/mL intermediate and MIC > 2 μg/mL characterized TGC resistant isolates. It was considered a microbiological cure when, using the same methodologies, the Gram-negative bacilli previously identified could not be recovered from the same (or related) body site after TGC treatment. We considered death caused by infectious process when the patient's death summary let it clear.

For evaluate the different therapeutic regimens, the standard dose of TGC was defined as 100 mg of dose of attack, followed by 50 mg (or proportional to weight) in maintenance. The high dose was defined as 200 mg of the attack dose and 100 mg or more in maintenance.

Previous use of polymyxins was defined as use of polymyxin B and/or sodium colistimethate prior to initiation of TGC therapy. When used concomitantly, it was defined as combination therapy, which is also applied to meropenem and amikacin.

In order to assess the clinical severity of the patients, the APACHE II (Acute Physiology and Chronic Health Evaluation II) or SAPS III (Simplified Acute Physiology III) scores were collected. APACHE II was gradually replaced by SAPS III in the Hospital, thus, any of the scores available on the patients' charts were collected, if these were calculated up to 30 days before or 15 days after the use of TGC.

2.4 Data colection: Data was collected from patient's electronic records. Demographic variables such as age and gender were considered. Clinical variables included neutrophil count; presence of comorbidities; hospitalization unit; scores APACHE II or SAPS III; site of infection. Therapeutic variables were the date of onset and end of use of TGC, dose of attack and maintenance; antimicrobials used up to 15 days before onset and during the use of TGC. Microbiological variables were the etiologic agent recovered from any body site prior to and after TGC use, as well as the susceptibility profile to TGC, polymyxin B, meropenem and amikacin. Outcomes were evaluated analysing the following variables: intra-hospital death within 30 days; intra-hospital death after 30 days of treatment; overall intra-hospital death and cause of death, defined by the medical team.

2.5 Statistical analysis: All statistical analyzes were conducted using the Statistical Package for the Social Sciences (SPSS®) software, version 18. The normal distribution of the quantitative variables was verified through the Shapiro-Wilk test. To test the differences between the groups (in relation to the maintenance dose of tigecycline) the Student's t-Test for independent samples (for variables with normal distribution) or the Mann-Whitney (for the variables that had the normal distribution rejected) were applied. The associations between categorical variables and groups of TGC doses are verified using the Qui-square test of independence. The Kaplan-Meier test was used to compare the survival function in the different outcome groups, using the non-parametric log-rank test. The level of significance used as acceptance or rejection criteria in the statistical tests cited above was 5% ($p < 0.05$).

Multivariate analysis was used to identify risk factors for mortality. For this analysis, we used Poisson regression.

3. Results

In this study, 87 clinical situations of TGC use were included for analysis, consisting of patients with a mean age of 41.4 ± 20.9 years and predominantly male (63.2%). Regarding the clinical characteristics, 19.5% of the patients presented severe neutropenia and 48.3% were exclusively or predominantly hospitalized in the ICU during the course of TGC. With the severity scores, the mean was 77.7 ± 21.8 for SAPS III and 23.7 ± 6.4 for APACHE II, calculated for 33 and 23 patients, respectively. Patients that had any positive culture totalized 85.5% (77 cases). The main sites of infection were the bloodstream (35.6%; 31 cases) and urinary tract (17.2%; 15 cases). Sites that have been classified as others (9.3 %; 4 cases) included meningeal, pelvis, diabetic foot and right upper limb abscess. The main comorbidity present in patients was the malignancy of hematological cells, with 34.5% of the cases. Among these malignancies there were acute and chronic myeloid leukemia, acute lymphoid leukemia, non-Hodgkin's lymphoma and myelodysplastic syndrome. The second most frequent comorbidity was solid organ transplantation, with 25.3% of the cases, including kidney, lung and heart transplantation. Certain comorbidities were classified as other (47.1%), including cystic fibrosis, acute cholecystitis, acute pancreatitis, adrenoleukodystrophy, systemic arterial hypertension, systemic lupus erythematosus, agranulocytosis, Sjögren's Syndrome, diabetes, congenital pure erythroid aplasia, amyloidosis, idiopathic aplastic anemia, among others. Patients that had more than one comorbidity represented 51.7%

Regarding the therapeutic characteristics, the median use of TGC was 10 days (Interquatile range - IQR: 6.0 – 15.0) and 30 cases (34.5%) used between 8 to 14 days. TGC was mainly used (67.8%) after the isolation of some bacteria. Most patients were previously exposed to meropenem (72.4%) and polymyxins (71.3%) prior to TGC treatment. Besides, 63.2% and 50.6% used meropenem and polymyxins, respectively, combined with TGC.

From the microbiological point of view, enterobacteria were the most isolated, with 90.9% (70 cases), even in pure culture or associated with other bacteria. *Klebsiella pneumoniae* was recovered in 67 cases (87.0%). The others enterobacterias was represented by two cases of *Enterobacter* sp. and one case of *Klebsiella oxytoca* (3.9%). About other agents isolated, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were recovered in pure culture in two cases, representing only 2.6% each. *Burkholderia cepacia* complex, *Achromobacter* sp and *Staphylococcus*. sp. coagulase negative strains isolated in pure culture representing only 3,9% of the bacterias. Among the microorganisms isolated, 63.9% and

69.7% were susceptible to TGC and amikacin, respectively. Isolates were susceptible to polymyxin B in 41.5% of cases and to meropenem in only 3.9%. In polimicrobial cultures, only enterobacteria was considered for susceptibility analysis. Regarding the outcomes, the overall intra-hospital mortality was 55.2% and 48.3% of the cases died within 30 days after the end of the TGC treatment. Of these cases that evolved to death, 89.6% had death related to the infectious process. Among the cases that performed culture after treatment (66.7%; 58 cases), the microbiological cure was achieved in 58.6% (34 cases).

Considering TGC dosage, two groups were considered (table 1): 44 patients received standard TGC dose and 43 received high dose. Those who received high dose were significantly more previously treated with meropenem compared to the group of standard dose (83.7% x 61.4%; p = 0.020). This was not true for polymyxins (79.1% x 63.6%; p = 0.112). Combined therapy with meropenem was also more frequent in high dose group (76.7% x 50.0%; p = 0.010), whereas polymyxins were combined with TGC in frequencies statistically similar (51.2% x 50.0%; p = 0.914).

Table 1. Analysis of the patients in the high dose group compared to the standard dose group.

Variables	Number of patients			
	Standard dose group (n = 44)	High dose group (n = 43)	Total (n = 87)	p valor
Demographic:				
Male sex, n (%)	25 (56.8)	30 (69.8)	55 (63.2)	0.210
Age, years, mean (SD)	40.4 (23.1)	42.4 (18.6)	41.4 (20.9)	0.656
Clinical characteristics:				
Severe neutropenia, n (%)	7 (15.9)	10 (23.3)	17 (19.5)	0.388
SAPS III, mean (SD)[a,b]	77.0 (22.0)	78.0 (22.2)	77.7 (21.8)	0.897
APACHE II, mean (SD)[c,d]	26.7 (5.4)	19.9 (5.8)	23.7 (6.4)	0.008
Hospitalization unit, n (%)				
ICU[e]	20 (45.4)	22 (51.2)	42 (48.3)	0.594
Clinic	10 (22.7)	7 (16.3)	17 (19.5)	0.448
Cirurgic	3 (6.8)	6 (13.9)	9 (10.3)	0.314
Bone marrow transplant	8 (18.2)	6 (14.0)	14 (16.1)	0.592
Oncological	3 (6.8)	1 (2.3)	4 (4.6)	0.616
Special cares	0 (0.0)	1 (2.3)	1 (1.1)	0.494
Site of infection, n (%)				
Bacteremia	13 (29.5)	18 (41.9)	31 (35.6)	0.230
Lung	10 (22.7)	2 (4.7)	12 (13.8)	0.018

Urinary tract	8 (18.2)	7 (16.7)	15 (17.2)	0.814
Abdomen	7 (15.9)	4 (9.3)	11 (12,6)	0.354
Bone	2 (4.5)	2 (4.7)	4 (4.6)	1.000
Others	0 (0.0)	4 (9.3)	4 (4.6)	0.055
Not informed	4 (9.1)	6 (14.0)	10 (11.5)	0.521
Comorbidities, n (%)				
Hematological cell malignancy	14 (31.8)	16 (37.2)	30 (34.5)	0.597
Bone marrow transplant	9 (20.5)	10 (23.3)	19 (21.8)	0.752
Solid organ malignancy	5 (11.4)	3 (7.0)	8 (9.2)	0.713
Solid organ transplant	6 (13.6)	16 (37.2)	22 (25.3)	0.011
Others	25 (56.8)	16 (37.2)	41 (47.1)	0.067
More than one comorbidity	23 (52.3)	22 (51.2)	45 (51.7)	0.918
Therapeutic characteristics:				
Days of use, median (IQR[f])	8.0 (5.0-13.0)	12.0 (7.0-21.0)	10.0 (6.0-15.0)	0.018
Use till 48 hours, n (%)	10 (22.7)	4 (9.3)	14 (16.1)	0.088
Use between 3 to 7 days, n (%)	11 (25.0)	8 (18.6)	19 (21.8)	0.470
Use between 8 a 14 days, n (%)	14 (31.8)	16 (37.2)	30 (34.5)	0,597
Use for more that 14 days, n (%)	9 (20.5)	15 (34.9)	24 (27.6)	0.132
Empirical use, n (%)	9 (20.5)	19 (44.2)	28 (32.2)	0.018
Previous use of meropenem, n (%)	27 (61.4)	36 (83.7)	63 (72.4)	0.020
Previous use of polymyxins, n (%)	28 (63.6)	34 (79.1)	62 (71.3)	0.112
Combined use of meropenem, n (%)	22 (50.0)	33 (76.7)	55 (63.2)	0.010
Combined use of polymyxins, n (%)	22 (50.0)	22 (51.2)	44 (50.6)	0.914
Microbiological characteristics:				
Etiologic agent isolated				
Enterobacteria[g]	34/40 (85.0)	36/37 (97.3)	70/77 (90.9)	0.110
Others[h]	6/40 (15.0)	1/37 (2.7)	7/77 (9.1)	0.110
Negative cultures	4/44 (9.1)	6/43 (14.0)	10/87 (11.5)	0.521
Distributions of MIC[i] for tigecycline, n (%)				
< 2,00 µg/mL	14/18 (77.8)	9/18 (50.0)	23/36 (63.9)	0.083
2,00 µg/mL	4/18 (22.2)	6/18 (33.3)	10/36 (27.8)	0.457
> 2,00 µg/mL	0/18 (0.0)	3/18 (16.7)	3/36 (8.3)	0.229
Isolates without MIC	22/40 (55.0)	19/37 (51.4)	41/77 (53.2)	0.749
Susceptibility, n (%)				
Tigecycline	14/18 (77.8)	9/18 (50.0)	23/36 (63.9)	0.083
Polymyxin B	11/31 (35.5)	16/34 (47.1)	27/65 (41.5)	0.344
Meropenem	2/39 (5.1)	1/37 (2.7)	3/76 (3.9)	1.000
Amikacin	24/39 (61.5)	29/37 (78.4)	53/76 (69.7)	0.110

Outcomes:				
Hospital				
Death within 30 days after treatment	21 (47.7)	21 (48.8)	42 (48.3)	0.918
Death after 30 days of treatment	3 (6.8)	3 (7.0)	6 (6.9)	1.000
Overall intra-hospital mortality	24 (54.5)	24 (55.8)	48 (55.2)	0.905
Discharge from hospital	20 (45.5)	19 (44.2)	39 (44.8)	0.905
Microbiological				
Bacteriological cure	17/27 (63.0)	17/31 (54.8)	34/58 (58.6)	0.531
Death related to the infectious process	23/24 (95.8)	20/24 (83.3)	43/48 (89.6)	0.348

Notes: [a]*Simplified Acute Physiology III*. [b]This variable was available for 12 patients in the standard dose group and 21 patients in the high dose group. [c]*Acute Physiology And Chronic Health Evaluation* II. [d]This variable was available for 13 patients in the standard group and 10 patients in the high dose group. [e]Intensive Care Unit. [f]Interquartile range. [g]Represented by 67 cases of *Klebsiella pneumoniae*, 2 cases of *Enterobacter* sp. and 1 case of *Klebsiella oxytoca*. [h]Represented by 2 cases of *Acinetobacter baumannii*, 2 cases of *Pseudomonas aeruginosa*, 1 case *of Burkholderia cepacia* complex, 1 case of *Achromobacter* sp. and 1 case of *Staphylococcus* sp. coagulase-negative. [i]Minimum Inhibitory Concentration.

The groups did not differed significantly in demographic characteristics. Regarding clinical characteristics, there was no significant difference in severe neutropenia, hospitalization units, SAPS III. However, mean APACHE II was significantly higher in the standard dose group (p = 0.008). About comorbidities, there were more cases of solid organ transplantation in the high dose group, with 37.2% (16 cases) vs. 13.6% (6 cases); p = 0.011, but the other comorbidities did not.

About the therapeutic characteristics, high dose group had longer TGC treatment (median = 12; IQR = 7 – 21 days) compared to standard one (median = 8; IQR = 5 – 21 days) and it was statistically significant (p = 0.018). Besides, those patients treated with high doses also received TGC empirically more frequently if compared with stantard dose's treated patients (44.2% and 20.5%; p = 0.018).

Overall intra-hospital mortality rate in both groups were statistically similar: 55.8% and 54.5%, for high and standard dose, respectively (p = 0.905), as well as bacteriological cure (24 and 24 cases; p = 0.531) and death related to the infectious process (20 and 23 cases;

p = 0.156). Using Kaplan-Meier curve analysis (figure 1 and figure 2), there was no evidence of a statistically significant difference in survival or discharge time between both groups (p = 0.649 and p = 0.496, respectively).

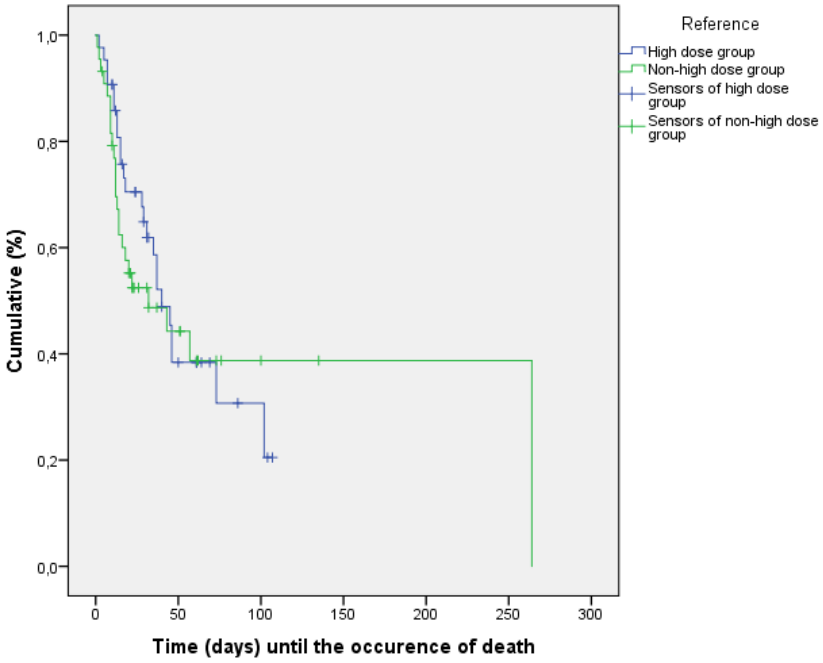

Figure 1. Kaplan-Meier curve for cumulative survival time analysis.

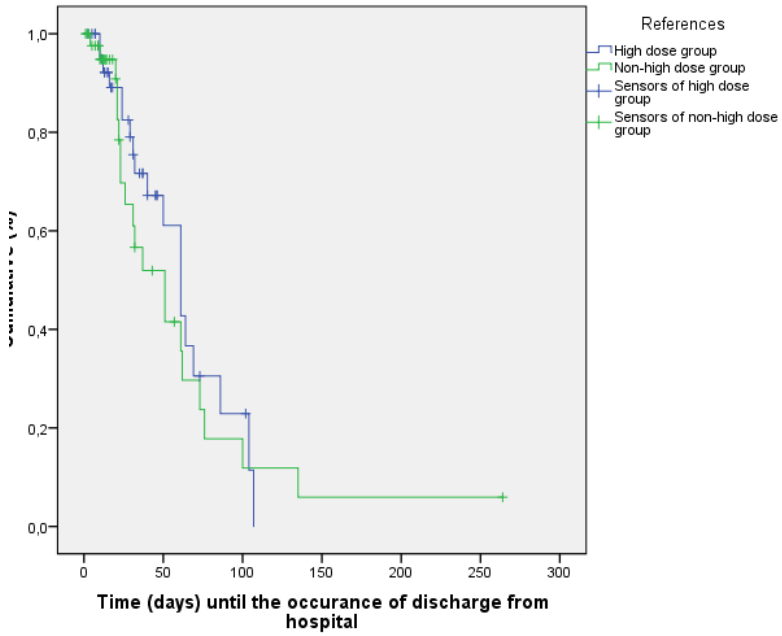

Figure 2. Kaplan-Meier curve for cumulative discharge time analysis.

Table 2 shows the results of the univariate analysis of factors associated with death. In this analysis, $p < 0.25$ was considered significant and, therefore, these variables were taken for multivariate analysis.

In this study, 48 episodes (55.2%) of TGC use had the death as outcome. Significant differences were observed between survivors and non-survivors regarding severe neutropenia, since patients who died had more of this condition (25.0 x 12.8; $p = 0.247$). There was also a significant difference in surgical ($p = 0.145$) and special care hospitalization units ($p = 0.009$); solid organ transplantation ($p = 0.140$) and hematological malignancy comorbidity ($p = 0.131$); and abdominal infection site ($p = 0.049$). Regarding the therapeutic characteristics, there was a significant difference between the previous use of meropenem ($p = 0.032$) and polymyxins ($p = 0.068$), as well as the combined use of these antibiotics ($p = 0.235$ and $p = 0.223$, respectively), being more frequent on the non-survivors group.

Table 2. Univariate analysis of factors associated with death.

Variables	Number of patients			
	Survivors group (n = 39)	Non-survivors group (n = 48)	p value	PR[a] (95% CI[b])
Demographics:				
Male sex, n (%)	21 (53.8)	34 (70.8)	0.925	1.031 (0.341-1.150)
Age, years, mean (SD)	39.6 (22.3)	42.9 (19.8)	0.824	1.002 (0.988-1.016)
Clinical characteristics:				
Severe neutropenia, n (%)	5 (12.8)	12 (25.0)	0.247	0.500 (0.155-1.615)
Hospitalization unit, n (%)				
ICU[c]	12 (30.8)	30 (62.5)	0.516	1.220 (0.670-2.221)
Clinic	9 (23.1)	8 (16.7)	0.274	0.588 (0.277-1.521)
Cirurgic	7 (17.9)	2 (4.2)	0.145	1.547 (0.860-2.783)
Oncological	2 (5.1)	2 (4.2)	-	-
Bone marrow transplant	8 (20.5)	6 (12.5)	0.689	0.809 (0.287-2.283)
Special cares	1 (2.6)	0 (0.0)	0.009	1.875 (1.168-3.010)
Site of infection, n (%)				
Bacteremia	14 (35.9)	17 (35.4)	0.777	0.902 (0.440-1.849)
Lung	4 (10.3)	8 (16.7)	0.335	0.444 (0.085-2.313)
Urinary tract	9 (23.1)	6 (12.5)	0.253	1.410 (0.782-2.541)
Abdomen	5 (12.8)	6 (12.5)	0.049	1.800 (1.003-3.229)

Others	1 (2.6)	3 (6.3)	0.858	0.875 (0.204-3.761)
Bone	2 (5.1)	2 (4.2)	-	-
Not informed	4 (10.3)	6 (12.5)	-	-
Comorbidities, n (%)				
Hematological cell malignancy	9 (23.1)	21 (43.8)	0.131	0.397 (0.120-1.316)
Solid organ malignacy	3 (7.7)	5 (10.4)	-	-
Solid organ transplant	11 (28.2)	11 (22.9)	0.140	1.547 (0.867-2.760)
Bone marrow transplant	5 (12.8)	14 (29.2)	0.468	0.542 (0.103-2.940)
Others	21 (53.8)	20 (41.7)	0.681	1.167 (0.559-2.436)
More than one comorbidity	18 (46.2)	27 (56.3)	0.828	0.926 (0.469-1.834)
Therapeutic characteristics:				
Days of use, meadian (IQR[d])	14,0 (7-19)	8,0 (4-12)	0.727	1.004 (0.983-1.026)
Use till 48 hours, n (%)	3 (7.7)	11 (22.9)	0.824	1.107 (0.452-2.708)
Use between 3 to 7 days, n (%)	7 (17.9)	12 (25.0)	0.469	1.293 (0.645-2.593)
Use between 8 to 14 days, n (%)	12 (30.8)	18 (37.5)	0.481	0.774 (0.380-1.578)
Use for more that 14 days, n (%)	17 (43.6)	7 (14.6)	0.836	1.071 (0.560-2.049)
Empiric use, n (%)	12 (30.8)	16 (33.3)	0.991	0.996 (0.469-2.116)
Previous use of meropenem, n (%)	23 (59.0)	40 (83.3)	0.032	0.545 (0.312-0.950)
Previous use of polymyxins, n (%)	24 (61.5)	38 (79.2)	0.068	0.586 (0.330-1.041)
Combined use of meropenem, n (%)	24 (61.5)	31 (64.6)	0.235	0.693 (0.378-1.270)
Combined use of polymyxins, n (%)	14 (35.9)	30 (62.5)	0.223	0.551 (0.211-1.436)
Microbiological characteristics:				
Etiologic agent isolated				
Enterobacteria	34/35 (97.1)	36/42 (85.7)	-	-
Others	1/35 (2.9)	6/42 (14.3)	-	-
Negative cultures	14/39 (35.9)	9/48 (18.8)	-	-
Distributions of MIC[e] for tigecycline, n (%)				
< 2,00 µg/mL	14/19 (73.7)	9/17 (41.2)	0.537	1.273 (0.591-2.740)

2,00 µg/mL	5/19 (26.3)	5/17 (29.4)	0.771	1.116 (0.533-2.334)
> 2,00 µg/mL	0/0 (0.0)	3/17 (17.6)	-	-
Isolates without MIC	16/35 (45.7)	25/42 (59.5)	-	-
Susceptibility, n (%)				
Tigecycline	14/19 (73.7)	9/17 (52.9)	0.537	1.273 (0.591-2.740)
Polymyxin B	13/31 (41.9)	14/34 (41.2)	0.782	0.857 (0.288-2.550)
Amikacin	25/35 (71.4)	28/41 (68.3)	0.493	0.782 (0.388-1.578)
Microbiologic outcome:				
Bacteriological cure	19/30 (63.3)	15/28 (5.6)	0.848	0.943 (0.464-1.881)

Notes: [a] *Prevalence ratio.* [b] Confidence interval. [c] Intensive Care Unit. [d]Interquartile range. [e]Minimum Inhibitory Concentration.

Regarding the multivariate analysis with Poisson regression (table 3), it was found that the combined use of meropenem, previous use of polymyxin and infection with abdominal site were predictors of overalll intra-hospital mortality.

Tabela 3. Multivariete analysis of risk factors for mortality.

Variable	p value	PR[a] (95% IC[b])
Tigecycline maintenance dose	0.155	1.738 (0.812-3.721)
Combined use of meropenem	0.016	2.435 (1.176-5.040)
Previous use of polymyxins	0.006	2.908 (1.363-6.206)
Abdomen	0.003	5.875 (1.834-18.706)

[a]Prevalence ratio. [b]Confidence intervals.

4. Discussion

The present study was designed to evaluate whether different therapeutic regimens of TGC could lead to better outcomes in critically ill patients. Our data showed that overall in-hospital mortality among the 87 cases after treatment with TGC was high (55.2%) and statistically similar between standard and high dose groups. Besides, in this study, patients who were treated with high doses did not live longer than those using standard regimens.

Geng *et al*. (2018) in a retrospective cohort study with n = 40 of patients with nosocomial bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae*, found a numerically lower mortality in the high dose group (200 mg attack dose, followed by 100 mg every 12 hours), with 52.2% vs. the group that used the standard dose (100 mg attack dose, followed by 50 mg every 12 hours), with 76.5% (p = 0.117), but with no significant difference. However, contrary to our findings, the authors showed a significantly longer survival time in patients in the high dose group (mean: 83 days vs. 28 days; p = 0.027). It is important to emphasize that our study contained in its sampling a larger and more similar n when dividing the groups. However, the mean APACHE II for the study of Geng *et al*. (2018) was 20.7 ± 9.4 in the high dose group, and in our study it was 19.9 ± 5.8, suggesting clinical similarity of disease severity.

In a retrospective study by De Pascale *et al*. (2014), patients with ventilator-associated pneumonia received TGC at doses of 50 mg every 12 hours or 100 mg every 12 hours, forming two subgroups with 30 and 33 patients, respectively. The major pathogens isolated were *Acinetobacter baumannii* and *Klebsiella pneumoniae* (28 and 30 cases, each). There was no significant difference in ICU mortality in the two groups, with 66.6% (20 cases) in the standard dose group and 48.4% (16 cases); p = 0.14.

Another retrospective study with 16 episodes of carbapenemase-producing *Klebsiella pneumoniae* infections by Moreno *et al*. (2014), compared the maintenance dose of TGC (100 mg vs. 200 mg per day) and there was no statistical difference in clinical response and outcome. The overall mortality of patients treated with 100 mg per day was 33.3% and at 200 mg per day was 20.0% (p = 0.55). The overall mean APACHE II at the start of TGC therapy in this study was 16.6 ± 5.2. In our sample, the mean score was 23.7 ± 6.4. This difference in severity may be related to the difference in mortality, which in the study by Moreno et al.

(2014) was only 25% in 30 days and, for us, it was 48.3% within 30 days after the TGC course and 55.2% overall.

Falagas and coworkers (2014) reviewed the efficacy and safety of therapeutic regimens containing high doses of TGC. They found that mortality in the cohort studies at the high dose (100 mg every 12 hours) ranged from 8.3% to 26%, while the low dose (50 mg every 12 hours) ranged from 8% to 61%, and varied according to the severity of the underlying infection. These data must be interpreted carefully because there were few studies for analysis in this systematic review. Ni *et al*. (2016) in a systematic review with meta-analysis found significantly lower ICU mortality in the high dose groups in the analysis of data from two studies, but, controversially, in the analysis of two other studies, there was no difference in mortality in 30 days. Similarly to the study cited above, Ni *et al*. (2016) also included few patients for analysis due to a shortage of studies.

The main justification for the use of high dose TGC is based on pharmacokinetic studies. The low maximum serum concentration of TGC compromises its use to treat infections with bacteremia in the previously approved therapeutic regimen, especially in the case of pathogens with high MIC, since it is important to have antibiotic concentrations above this level for therapeutic success (Giamarellou and Poulakou, 2011). Bloodstream infections were highly prevalent in our case series (35.6%; 31 cases). Borsuk-De Moor and coworkers (2018) also studied critically ill patients. They evaluated pharmacokinetics of high-dose TGC in patients with sepsis and septic shock, with 37 adult ICU patients receiving an attack dose of 200 mg, followed by 100 mg every 12 hours. The developed model, however, did not show that there is a need for dose adjustment based on the available covariates of the patients.

As mentioned previously, in infections with pulmonary focus, one of the most prevalent in our study (13.8%; 12 cases), the concentration of TGC in the pulmonary epithelial fluid may be lower than needed, leading to the inability of microbiological cure based on the pathogen MIC (Burkhardt *et al*., 2009). Indeed, Xie *et al*. (2013) in a pharmacokinetic/pharmacodynamic analysis of TGC, observed excellent *in vitro* activity but *in vivo* standard dose failure for resistant strains, including *Acinetobacter baumannii*, *Enterobacter* sp. and *Klebsiella pneumoniae*.

We recognized many limitations in our study, such as the retrospective nature, and the low number of patients in each group. The major limitation, however, is the fact that we

analysed a heterogeneous group of patients considering type of infection, which may create a confounding factor, once infections may be highly variable in severity and life-threatening. Besides, we were not able to relate MIC and outcome (death or survival) because our limited number of patients. This is a limitation as dose regimens of TGC is a subject of major concern and the outcomes of this antibiotic treatments may be highly influenced by microrganisms and pharmacokinetics/pharmacodinamics characteristics, such as MIC and site of infection. Increasing the number of patients presenting infections and including those with variable MICs will improve our statistical analysis, such as a subgroup analysis, only with patients with *Klebsiella pneumoniae* bacteremia, wich represents the most prevalent microorganism and site of infection in our study.

5. Conclusion

Despite limitations described above, in this study, there was no greater benefit in the use of high doses of TGC, since there was no statistically significant difference in intra-hospital mortality and time survival among groups. Studies with a more robust design should be performed, since the importance of TGC use can not be ruled out mainly considering infections caused by multiresistant pathogens.

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Declarations of interest: none

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Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

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• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

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A concise and factual abstract is required. It should be 150 words or less for full-length papers and 50 words or less for notes. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

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Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of').

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Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

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List funding sources in this standard way to facilitate compliance to funder's requirements:

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[dataset] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015.

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Journal abbreviations source

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