ORIGINAL RESEARCH

High-Dose Tigecycline in Elderly Patients with Pneumonia Due to Multidrug-Resistant *Acinetobacter baumannii* in Intensive Care Unit

Xiang-Rong Bai[1,2]
De-Chun Jiang[1,2]
Su-Ying Yan[1,2]

[1]Department of Pharmacy, Xuanwu Hospital Capital Medical University, Beijing, People's Republic of China; [2]National Clinical Research Center for Geriatric Disorder, Beijing, People's Republic of China

Purpose: The association between clinical and microbiological outcomes and high-dose tigecycline (TGC) was assessed in elderly (≥60 years old) patients with hospital-acquired and ventilator-associated pneumonia due to multidrug-resistant *Acinetobacterbaumannii* (*A. baumannii*). This study also assessed tigecycline combination with different antibiotics and its influence on the outcome.

Patients and Methods: An observational retrospective cohort study was conducted. Patients over 60 years old were treated with standard-dose (SD) TGC (100-mg intravenous TGC initially, followed by 50-mg doses administered intravenously twice daily) and high-dose (HD) TGC (200-mg intravenous TGC initially, followed by 100-mg doses administered intravenously twice daily) for a microbially confirmed infection. The outcome was 30-day crude mortality, co-administered antimicrobial agent and the microbial eradication percentage in both groups.

Results: A total of 48 multidrug-resistant *A. baumannii* respiratory patients were identified. Tigecycline was administered to 85% of ventilation-associated pneumonia (VAP) patients (28/33) in the SD group and 80% of VAP patients (12/15) in the HD group. Combined therapy was the major treatment option in both groups, accounting for 85% and 87%, respectively. Median treatment duration in both groups was 7.36 vs 8.6 days, respectively. Survival days were 13.61 vs 12.4 days (*P*=0.357), respectively. The 30-day crude mortality was 39.4% (13/33) for the SD group and 14% (2/15) for the HD group (*P*=0.098). The microbial eradication rate of respiratory specimens in the SD group was higher than that in the HD group (*P*=0.02). The variables associated with 30-day crude mortality were chronic obstructive pulmonary disease (hazard ratio [HR] 11.63, 95% CI 1.094–123.058; *P*=0.042), tigecycline treatment duration (HR 0.690, 95% CI 0.515–0.926; *P*=0.013), and surgery before infection (HR 79.276, 95% CI 6.983–899.979; *P*=0.000). High-dose tigecycline was not associated with 30-day crude mortality (adjusted HR 0.329, 95% CI 0.074–1.460; *P*=0.145). Combined antibiotics was also not different between the two groups.

Conclusions: High-dose tigecycline was not associated with 30-day crude mortality in elderly patients with pneumonia due to multidrug-resistant *A. baumannii*, although the microbial eradication rate was high.

Keywords: pneumonia, critical ill patients, high-dose tigecycline, drug-resistant, *Acinetobacter baumannii*

Introduction

Nosocomial pneumonia is a leading cause of death in critically ill patients.[1] One of the most common pathogens of nosocomial pneumonia is *Acinetobacter baumannii* (*A. baumannii*). The prevalence of multidrug-resistant (MDR) or extensively drug-

Correspondence: De-Chun Jiang
Email jiangdechun@sina.com

resistant (XDR) *A. baumannii* has increased to at least 80% in the past decades.[2] *A. baumannii* is the most commonly isolated from endotracheal aspirates.[3] Patients hospitalized in the intensive care unit (ICU) mostly received wide spectrum antibiotic treatment leads to isolation of *A.baumannii* strains frequently.[4] Empirical coverage of *A. baumannii* is recommended for severe infections (severe sepsis or septic shock) in the ICU.[5] Considering the efficacy of various antimicrobial treatments for MDR/XDR *A. baumannii* pneumonia, guided selection of an optimal antimicrobial treatment for this infection is urgently needed.

Tigecycline is a bacteriostatic activity against multidrug-resistant (MDR) *A. baumannii* group.[6] A retrospective study shows that the relatively low clinical success rate and high microbial eradication rate were observed for multidrug-resistant *A. baumannii* infection.[7] International guidelines considered tigecycline as second-line antibiotic therapy.[8] Infectious Diseases Society of America guideline recommended against the use of tigecycline for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) because current label dose worsened clinical outcomes.[9] However, tigecycline was low level of resistance for *A. baumannii* in China.[10] Publish data showed that high-dose tigecycline was associated with clinical outcomes and survival time.[11] A meta-analysis indicated high-dose tigecycline was more effective than standard-dose tigecycline or the comparators for the treatment of HAP.[12] It also may be used higher-than-licensed dosing such as 100mg twice daily for infections due to MDR in critical care.[13] A recent meta-analysis indicated that high-dose tigecycline reduced all-cause mortality in nosocomial-acquired pneumonia.[14] But, the main pathogens were Klebsiella pneumoniae. In fact, the clinical efficacy of high-dose tigecycline is unknown for elderly patients. So we conducted a retrospective cohort study to determine clinical and microbial outcomes in elderly patients treated with high-dose vs standard-dose tigecycline for severe infections caused by MDR Gram-negative *A. baumannii*.

Patients and Methods
Study Design and Patients
The retrospective cohort study was conducted at the 6 ICU of Xuan Wu Hospital Capital Medical University, a 1100-bed, academic, tertiary care medical centre in China. Data were collected between 1 January 2016 and 31 December 2017 in medical records. The inclusion criterion was critical patients ≥60 years of age.

Respiratory specimens for Gram stain and culture were obtained via endotracheal aspirate (ventilated patients), expectorated or induced sputum (non-ventilated patients) before using of TGC.[15] The pathogens were *A. baumannii* and simultaneous empirical tigecycline had been given. Results of 2 times ≥3+colony forming units were considered as positive bacterial culture.[16] Patients diagnosed with hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) which was defined as pneumonia with an onset 48 h or longer after admission. Ventilator-associated pneumonia was defined as parenchymal lung infection with an onset 48 h or longer after endotracheal intubation and mechanical ventilation according to the guidelines.[17] Patients were stratified to two treatment groups: (1) standard-dose (SD) of patients was treated with loading dose (LD) TGC 100mg, followed by maintenance dose (MD) 50 mg administered intravenously twice daily, for at least 5 days) and (2) high-dose of (HD) patients was treated with loading dose (LD) TGC200 mg, followed by maintenance dose (MD) 100mg administered intravenously twice daily, for at least 5 days). Exclusion criteria were as follows: <60 years of age; pregnant women; severe liver dysfunction (Child-Pugh class C); treated with vancomycin and anti-fungal medications. The study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (NO2018003). This dataset exempted from patient consent owing to retrospective medical data, in which patients cannot be contacted directly. Clinical diagnosis and treatment were collected in the medical records, except patients' names. We have confidential measures for the privacy of patients. This work was conducted according to the provisions of the Declaration of Helsinki.

Study Variables
Data were collected upon ICU admission and at the start and end of tigecycline treatment. Only patients who received tigecycline therapy for at least 5 days were included. Patients who began tigecycline therapy before culture were considered empirical therapy. Survival time was calculated from the time tigecycline therapy was initiated. Clinical data were collected, including demographics, the Charlson index,[18] the Mean Acute Physiology and Chronic Health Evaluation (APACHE) II score,[19] the nosocomial pneumonia source,[20] surgery before infection and septic shock before antibiotic therapy.[21] Data on microbiological and clinical outcomes

and concomitant antimicrobial agents (carbapenem, aminoglycosides, Beta-lactamase) were also collected.

Microbiological Data

Antibiotic susceptibility profiling of the isolates was performed using the Vitek 2 system (bioMérieux, Marcy-l'Etoile, France). Tigecycline susceptibility breakpoints were determined according to the FDA standard (MIC <2mg/L, sensitive; MIC ≥8mg/L, resistant) by using the E-test method (BIO-KONT, Wenzhou, China).[22,23] Multidrug-resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories; extensive drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories.[24–26] The MDR/XDR infection was determined according to the results of the bacterial culture and clinical symptoms.[27]

Outcomes

The primary outcome measure in this study was 30-day crude mortality after TGC treatment, and the secondary outcome measure was assessed pathogen eradication. Thirty-day crude mortality, defined as the incidence of deaths from any cause in the ICU within the approximately 30-day follow-up duration, was chosen as the primary outcome variable for comparing antimicrobial effectiveness.[28] Microbial eradication was defined as no growth of *A. baumannii* or susceptibility change from MDR strains to susceptible strains in *A. baumannii* in follow-up respiratory tract cultures before and 7 days after treatment cessation.[29] Two physicians who are blinded to the treatment to evaluate the outcome, and when judgments are discordant (about 5% of patients), the results reassessed by other physicians to reach a consensus decision.

Statistical Analysis

Continuous data are presented as the median and interquartile range (IQR), and categorical data are presented counts and percentages. The Kolmogorov–Smirnov test was used to evaluate the distribution of the variables. Non-normally distributed data were assessed using the Mann–Whitney test, and the median and selected centile (25th to 75th) values are provided. Normally distributed data were assessed using Student's *t*-test. Categorical variables are presented as proportions and were analysed using the chi-square test or Fisher's exact test, as appropriate. A P-value <0.05 was considered significant. The

crude odds ratio (OR) and 95% CI were calculated for each variable. We used Kaplan–Meier survival curves to show the patients' cumulative survival rates, and the Log-rank test was used to compare patient survival rates between the two groups. Cox regression analyses were performed to evaluate factors independently influencing clinical outcomes. All statistical analyses were performed using SPSS, version 23, for Windows (SPSS, Chicago, IL, USA).

Results
Patient Characteristics

During the study period, forty-eight elderly patients were included: 33 patients in the standard-dose (SD) group and 15 in the high-dose (HD) group (Table 1). The mean ages were 77.64±9.26 years and 70.33±9.01 years without significant differences between study groups (*P=0.093*). The pneumonia sources were hospital-acquired or ventilator-acquired. The sources did not differ between the SD TGC and HD TGC groups. No significant differences were noted between the Charlson index and APACHE II scores in both groups, which suggested that the disease severity baselines were similar. Patients in the two groups with chronic obstructive pulmonary disease (COPD) did not differ (*P*=0.103). Previous carbapenem use and hospital stay before treatment did not differ between groups.

Primary and Secondary Outcome Outcomes

The number of 30-day deaths did not significantly differ between the two groups (*P*= 0.098). Survival days and number of hospital days did not differ. Microbiological eradication percentages were higher when TGC was used at higher doses (61.5% versus 66.7%; *P* =0.02) (Table 2)

Combined Various Antimicrobial Medication

We also analysed the combined *antimicrobial* medication in both groups (Table 3). Combined carbapenems were more frequent in the high-dose TGC group (*P* =0.017). Combined antibiotics did not differ between the two groups, but no patients had combined antibiotics in the HD TGC group. No specific antibiotic combination was associated with a better outcome.

Table 1 Demographic Characteristics of the 48 Elderly Patients with the Standard-Dose (SD) and High-Dose (HD) Tigecycline

Variables	SD TGC Group (n = 33)	HD TGC Group (n = 15)	P-value
Age (years), mean ± SD	77.64±9.26	70.33±9.01	0.993[a]
Gender (male: female)	22/11	13/2	0.182[b]
Weight (kg) mean ± SD	64.83±15.31	73.60±13.49	0.067[a]
Source of Pneumonia			
Hospital-acquired	5 (15.0%)	3 (20.0%)	0.685[b]
Ventilator-associated	28 (85.0%)	12 (80.0%)	
Co-morbidities			
COPD	9 (27.3%)	1 (6.7%)	0.103[b]
Invasive Procedures			
Tracheotomy	2 (6.0%)	4 (26.7%)	0.067[b]
Parenteral nutrition	10 (30.3%)	5 (33.3%)	0.543[b]
Hospital stay before treatment	15.15± 9.08	14.47± 11.46	0.550 [a]
Previous carbapenem use	26 (78.8%)	10 (66.7%)	0.476[b]
Days of tigecycline use	7.36±2.41	8.6±1.10	0.476[b]
Charlson index	3.39±2.04	3.07±2.15	0.616 [a]
APACHE II score	18.69±5.75	17.47±3.95	0.457[a]
Septic shock	7 (21.2%)	0	0.086[b]

Notes: Data are expressed as absolute frequencies (n) and percentages (%). *Statistically significant ($P \leqq 0.05$). [a]Analysis of variance. [b]Chi-square test.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation.

Predictors of 30-Day Crude Mortality in Patients

Univariate regression analysis (Table 4) of the 48 patients showed that individuals with clinical failure were older, had COPD, longer lengths of hospital stay and TGC treatment and surgery duration before infection. Cox regression analysis indicated that COPD independently

Table 2 The Primary and Secondary Outcomes in Both Groups

Variable	SD TGC Group (n = 33)	HD TGC Group (n = 15)	P-value
Death at 30 days	13 (39.4%)	2 (13.3%)	0.098[b]
Survival days	13.61±11.48	12.4±7.37	0.357[a]
Number of hospital days	28.76±13.49	26.87±12.41	0.631[a]
Microbiological eradication	8 (61.5%)	10 (66.7%)	0.02*[b]

Notes: Data are expressed as absolute frequencies (n) and percentages (%). *Statistically significant ($P \leqq 0.05$). [a]Analysis of variance. [b]Chi-square test.

Table 3 Combined Various Antimicrobials in Both Groups

Variable	Target Therapy		P-value
	SD TGC Group (n = 33)	HD TGC Group (n = 15)	
Tigecycline combined with various antimicrobial	28 (84.8%)	14 (93.3%)	0.650[a]
Carbapenems	12 (30.3%)	11 (73.3%)	0.017*[a]
Aminoglycosides	1(3.03%)	1 (6.7%)	0.545[a]
Beta-lactamase	16 (39.4%)	2 (13.3%)	0.054[a]

Notes: Data are expressed as absolute frequencies (n) and percentages (%). *Statistically significant ($P \leqq 0.05$). Carbapenems: Imipenem; meropenem; biapenem. Aminoglycosides: amikacin. Beta-lactamase: cefepime; ceftazidime; piperacillin and sulbactam. [a]Chi-square test.

predicted 30-day mortality (HR 11.63, 95% CI 1.094–123.058) and surgery before infection (HR 79.276, 95% CI 6.983–899.979). The predictor was days of tigecycline use (HR 0.690, 95% CI 0.515–0.926).

Table 4 Cox Regression Analysis of Factors Associated with 30-Day Mortality in 48 Elderly Patients

Variable	Multivariate Analysis		
	HR	95% CI	P-value
COPD	11.63	(1.094–123.058)	0.042*
Tigecycline use of days	0.690	(0.515–0.926)	0.013*
Surgery before infection	79.276	(6.983–899.979)	0.000*

Note: *Statistically significant ($P \leqq 0.05$).
Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.
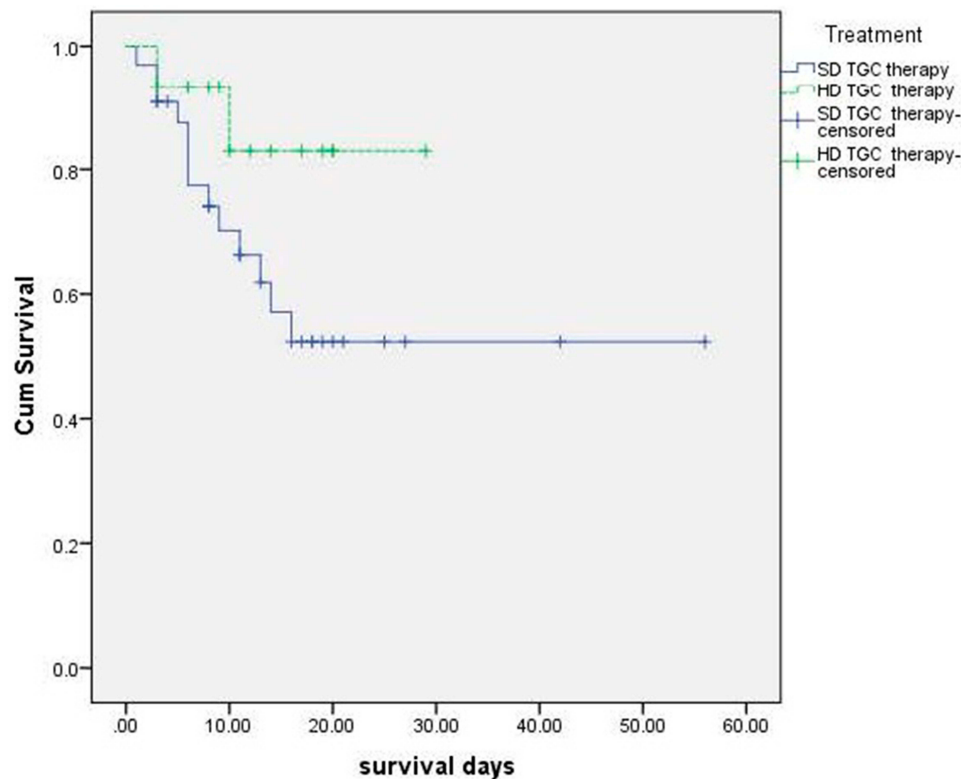
Figure I Kaplan–Meier curves for mortality as a function of SD TGC or HD TGC by survival days.

Our study also analysed 30-day follow-up patient survival in both groups (Figure 1). A Log-rank test comparison confirmed no significant difference in 30-day survival (Log-rank test 2.414, $P= 0.12$).

Discussion

All patients in this study were elderly and diagnosed with nosocomial pneumonia. In this retrospective study, we collected the patient comorbidities, disease severity (Charlson index, APACHE II score),[30] invasive procedures (tracheotomy, parenteral nutrition), status (sepsis), and co-administered antibiotics, which has an association with mortality in ICU.[31] No statistically significant differences were seen in these variables for both groups.

In this study, we found that there was no significant difference between the two groups in the 30-day deaths. The high dose of TG did not improve the survival days and number of hospital days for the elderly. A meta-analysis study indicated that all-cause mortality was higher in the tigecycline group than in the other groups, but the difference was not significant (odds ratio 1.28, 95% CI 0.97–1.69).[32] Our previous meta-analysis results indicated that there was no significant association between high dose of TGC and

mortality.[33] A review study showed that mortality with high-dose tigecycline in the cohort studies ranged from 8.3% to 26%, while mortality in the low-dose groups (50 mg q12 h) ranged from 8% to 61% and depended on the underlying infection severity. Available data are limited regarding the effectiveness and safety of high-dose tigecycline.[34] A recent network meta-analysis of *A. baumannii* studies compared the efficacy of fifteen antimicrobial treatments for drug-resistant *A. baumannii* pneumonia in critically ill patients. For survival benefit, sulbactam monotherapy appeared to be the best treatment, high-dose tigecycline was not preferred.[35]

Our study indicated that the eradication rate in the HD TGC group was significantly higher than in the SD HGC group. Synergistic effect against MDR *A. baumannii* with the combination of sulbactam and carbapenem had been reported.[36] A combination with carbapenem is more frequent in the HD TGC group than SD TGC group. So, it may play a role in giving a high airway eradication rate. However, tigecycline group had a lower microbiological eradiation rate comparison with other control groups.[37] Some scholars have suggested that combination therapy may be an option.[38] However, combined therapy with two active drugs was superior to therapy with a single active drug.[39] The study showed TGC combination

therapy did not improve microbiologic eradication or all-cause mortality. It can only be recommended when other optimized therapeutics, such as colistin, are unavailable.[40] An observational cohort study included colistin monotherapy (9 million UI/day) or combined therapy with colistin and tigecycline (100 mg/day) and found the combined targeted therapy with high-dose colistin and standard-dose tigecycline was unassociated with a lower 30-day crude mortality of bacteremia due to carbapenem-resistant *A. baumannii* in critically ill patients.[41] A study showed 42 patients with XDR *A. baumannii* infection randomized into two groups: the tigecycline group and the tigecycline and cefoperazone-sulbactam (1:1) group. The total combined efficacy rate (including all patients who demonstrated improved conditions) was significantly higher in the tigecycline and cefoperazone-sulbactam.[42] In vitro synergistic activities of tigecycline combined with cefoperazone-sulbactam against MDR *A. baumannii* were demonstrated.[43] This combination may be an option for critically ill patients; however, due to the small number of current research samples, a large clinical trial is needed to verify the best combination.

In our study, COPD and surgery before infection were associated with 30-day mortality. Survival analysis found high-dose tigecycline was unassociated with lower crude mortality. A study indicated thatThe microbial success was 21.0 times higher for every 1g/dl increase in albumin ($P<0.001$) and 8.59 times higher for patients without VAP compared to those with VAP ($P<0.003$).[44] Although total protein generally is unaffected by aging, the plasma albumin portion has been shown to decrease from 4 g/dL in young adults to approximately 3.5 g/dL in patients over 80.[45] This may also explain tigecycline's poor efficacy in elderly patients.

Several potential limitations should be considered when interpreting these results. First, the number of subjects included was small. Second, we did not assess the impact of high-dose tigecycline on adverse drug reactions such as the rate of abnormal laboratory measures or patients requiring TGC discontinuation. One study showed high-dose tigecycline-associated alterations in coagulation parameters, such as the plasma-fibrinogen concentration, international normalised ratio (INR) and activated partial thromboplastin time (aPTT), especially in elderly patients.[46,47] Third, we also did not analyze the clinical response. Fourth, the different number of patients and number of carbapenem combinations in both groups were also heterogeneity in this study.

In conclusion, high-dose tigecycline was unassociated with lower crude mortality in elderly patients with pneumonia due to multidrug-resistant *A. baumannii*, and it benefitted eradicating *A. baumannii* in the ICU.

Combination therapy may be an option. Prospective cohort studies or random clinical trials are needed to confirm these preliminary results.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ICU, intensive care unit; HR, hazard ratio; SD; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Disclosure

The authors declare no conflicts of interest in this work.

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