Tropical Journal of Pharmaceutical Research July 2018; 17 (7): 1407-1413
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v17i7.26

Original Research Article

Etiologic analysis of Chinese patients with agranulocytosis and hematopathies infected with resistant bacteria: Anti-bacterial effect of tigecycline

Feifei Che*, Chunqian Wan, Xiaodong Wang, Jiao Chen, Juan Huang
Department of Hematology, Sichuan Academy of Medical Science and Sichuan People's Hospital, Chengdu, 610072, China

For correspondence: **Email: feifeiche@cntv.cn; **Tel:** 0086-28-87732855; **Fax:** 0086-28-87732855*

Sent for review: 17 November 2016 *Revised accepted: 17 June 2018*

Abstract

Purpose: *To assess the etiologic characteristics of resistant bacterial infections occurring in agranulocytosis patients with hematopathies, and to determine the effect of tigecycline (TGC).*
Methods: *After ineffective treatment with carbapenem, all of the patients were divided into the following three groups: TGC alone (15 cases); TGC as initial treatment, followed by a combination with other antibiotics (40 cases); and TGC in combination with other antibiotics from the start of treatment (71 cases).*
Results: *Among the 126 patients, 108 had fevers (85.71 %). The most common infection site was lung, accounting for 71.43 % of all infections. A total of 52 pathogens were isolated from 126 hospitalized patients, including 38 Gram-negative bacteria (70.37 %), 14 Gram-positive bacteria (25.93 %), and 2 fungi (3.70 %). TGC treatment efficacy was 50.79 %. There were no statistically significant differences between the three treatment groups (p = 0.473). Adverse drug reaction was nausea and vomiting (14.29 %), nausea without vomiting (11.90 %), diarrhea (6.35 %), and generalized skin rash with itching (3.17 %).*
Conclusion: *TGC is effective in treating neutropenic patients with hematopathies who are infected with resistant bacteria. The side effects of TGC are few; thus, TGC is safe and generally well-tolerated.*

Keywords: *Tigecycline, Agranulocytosis, Resistant bacteria, Hematopathy, Neutropenic patients*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

After treatment with different chemotherapy regimens, patients with hematologic malignancies may show varying degrees of bone marrow suppression, immunosuppression, intestinal mucosal barrier damage [1], and risk of infections. Immunosuppression, using broad-spectrum antibiotics, and immunosuppressants are usually correlated with an increased appearance of antibiotic-resistant bacteria [2]. There has been a significant increase in the incidence of multi-resistant microorganisms, which were the main causes of death in patients with hematological malignancy [3, 4]. As the effect of bacterial cultures is low and time-consuming, the introduction of empiric antibiotic therapy to prevent and control infections in the

early stages is important to improve the survival rate of patients with hematopathies.

Tigecycline (TGC) is the first available antimicrobial agent in a new class of antimicrobials, which was called TGCes, which are structurally similar to tetracyclines. Compared with tetracycline, TGC provides a broader antimicrobial spectrum and lower susceptibility to resistance development with the special structure by itself. TGC offers a broader anti-microbial spectrum and a lower susceptibility for the occurrence of resistance than tetracyclines. TGC has an activity against of multiple drug resistance (MDR) bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL), *Klebsiella pneumoniae,* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp), and the *Acinetobacter baumannii* group [5]. TGC has been licensed for the treatment of complicated intra-abdominal infections (cIAIs), complicated skin and soft tissue infections (cSSTIs), and community-acquired pneumonia (CAP). There are limited reports on the use of TGC in patients with granulocytosis with drug-resistant bacterial infections.

Based on recent studies, TGC has several advantages: (a) TGC's broad-spectrum activity includes gram-positive, gram-negative, anaerobic and atypical pathogens, except for *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Mortierella molhid* and *Providencia*. TGC also has a broad spectrum of activities, including MDR/XDR Gram-positive and negative bacteria, with the exception of *Pseudomonas*. [15-17]. (b) Because of the special structure, TGC meets the urgent need to overcome the deteriorating antimicrobial drug resistance by overcoming ribosomal protection and effective drug efflux resistance mechanisms [18]. (c) Lower liver and kidney toxicity for patients complicated by liver or kidney disease. (d) The side effects are well-tolerated.

TGC is a safe and efficacious antibiotic for treating infections caused by XDR or MDR bacteria; however, few studies have systemically investigated the benefits resulting from TGC treatment in neutropenic adult patients with hematopathies infected with resistant bacteria. A retrospective study of a TGC-based treatment approach was performed to analyze the curative effect and safety of TGC to treat agranulocytosis patients suspected to have resistant bacterial infections.

METHODS

Study design

The medical records of agranulocytosis patients with resistant bacterial infections, who were treated in the Hematology Department of Sichuan People's Hospital (ChengDu, China) between October 2010 and October 2015 were retrospectively reviewed. This study was approved by the Ethics Committee of Sichuan Academy of Medical Science and Sichuan People's Hospital for Human Research in accordance with International ethical guidelines for biomedical research involving human subjects[19] and Declaration of Helsinki promulgated in 2013 (Ethical review(research) No. 25, 2015) [20].

Clinical data collection

Consecutive patients of any age with hematopathies who were admitted with neutropenia and documented cultures of resistant bacteria were enrolled in the study. Access to clinical data including age, gender, underlying disease, severity of neutropenia, presence of central venous catheters, organisms isolated from the blood and antimicrobial susceptibility, administration of antibiotics, efficacy and safety.

Bacteriologic identification and antimicrobial susceptibility evaluation

Culture samples were obtained from the peripheral blood, catheter blood, and other sites of infection. Disk diffusion technology is used for bacterial identification. Sensitivity tests were performed using the Microscan system (Dade Behring, West Sacramento, CA, USA) and the results were interpreted according to the CLSI guidelines published in 2012 [6].

Definitions

Fever is defined as the mouth temperature of 38.3 ° C or the mouth temperature of 38 ° C for 1 hour [7]. Neutropenia was defined as an absolute neutrophil count (ANC) < 500/mm^3 or < 1000/mm^3 and was expected to drop to < 500/mm^3 within 2-3 days. Severe neutropenia was defined as ANC < 100/mm^3 [8,9]. Multi-drug resistant (MDR) was diagnosed when no susceptibility to no less than three antimicrobial categories.

According to the consensus of European experts, extensive resistance (XDR) is defined as resistance to not less than one agent but up to

two classes of antimicrobial agents [10]. Bloodstream infection (BSI) was considered, when it was hospital-acquired, healthcare-related, according to the criteria described previously [11]. The catheter-related bloodstream infection (CRBSI) was considered to be a bloodstream infection in patients with intravascular catheters or catheter removal within 48 hours, with fever, chills or hypotension and no other source of infection.

Treatment

After ineffective treatment with a carbapenem antibiotic, all of the patients were treated with TGC for resistant bacterial infections and concurrent granulocytopenia, and divided into three groups according to the drug regimen: TGC alone (15 cases); TGC as initial treatment, followed by a combination with other antibiotics (40 cases); and TGC in combination with other antibiotics from the start of treatment (71 cases).

TGC was administered intravenously (40-60 min drip infusion) at an initial dose of 100 mg and a maintenance does of 50 mg every 12h. The entire course of treatment was 5-7 days in length. When the body temperature was normal, step-down treatment was initiated or the drug was discontinued.

Clinical outcome

The clinical response was determined based on the investigator's judgement. They specified the success or failure of the treatment according to commonly used clinical practice criteria. When the symptoms and signs are completely relieved or improved, consider the clinical response chosen. The patient was cured or improved, and there was no need to change treatment regimen.

A lack of serious adverse effects leading to discontinuation of treatment could also be considered as a favorable clinical response. When the clinical signs and symptoms of infection persist or worsen, or when new signs or symptoms were acquired. Therefore, another class of antibiotic was added to the treatment regimen or there was a change to an alternative antibiotic regimen.

Statistical analysis

Statistical analyses were primarily descriptive using a χ^2 test. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS (version 16.0; SPSS, Inc., Seoul, Korea).

RESULTS

Patient characteristics

A total of 126 patients (62 females and 64 males) who were infected with resistant bacteria and treated with TGC were documented. Table 1 lists the baseline characteristics of patients. All patients showed neutropenia at time of infection. Number of male and female was almost equal. Most patients with neutropenia suffer from acute myeloid leukemia (83.3 %). Central venous catheters (100 %), high-dose chemotherapy (28.57 %), immune-suppressive therapy (15.08 %), and diabetes mellitus (15.08 %) were the 4 main reasons for infection with resistant bacteria in the 126 patients. Among the 126 patients, 108 had fevers (85.71%), and the most common infection site was the lung (71.43 %).

Microbiologic activity

Fifty-four strains of bacteria were obtained from 126 hospitalized neutropenic patients with hematopathies. The majority of strains 38 of 54 (70.37 %) were Gram-negative bacteria. The most commonly found Gram-negative and -positive organisms were Enterobacteriaceae and staphylococci (CoNS), respectively. We also observed 2 fungi (3.70%). The pathogens and the frequencies were shown in Table 2.

TGC administration

TGC was used according to the manufacturer's instructions with an initial dose of 100 mg and then 50 mg every 12 hours. Despite the use of broad-spectrum antibiotics, all patients with persistent fever or worsening signs of infection were treated with TGC. TGC was used for 10 days (range 1-28 days). Fifteen patients received TGC monotherapy, 40 patients received TGC as initial treatment followed by combination with other antibiotics, and 71 patients received TGC combined with other antibiotics from the start of treatment. The antibiotic therapy regimens are listed in Table 3.

Response and duration of therapy

The TGC response rates are shown in Table 4. Among 64 (50.79 %) patients, the TGC treatment was successful. The median duration in the patients with good responses to the TGC treatment till defervescence was 2.13 days (range, 0-6 days). There was no significant difference in the efficacy of TGC monotherapy and combination therapy ($p = 0.473$),

Table 1: Patient characteristics

Characteristic		Patients (N=126)	Frequency (%)
Gender	Male	64	50.79
	Female	62	49.21
Age（years）	≥18	108	85.71
	<18	18	14.29
Absolute neutrophil count ($\times 10^9$/L)	<0.2	104	82.54
	0.2~0.5	22	17.46
Diagnosis	Acute leukemia	105	83.33
	Myelodysplastic syndrome	9	7.14
	Multiple myeloma	4	3.17
	Lymphoma	3	2.38
	Severe aplastic anemia	3	2.38
	Hemophagocytic syndrome	2	1.59
Infection factors	Central venous catheter	126	100.00
	High-dose chemotherapy	36	28.57
	Immunosuppressive therapy	19	15.08
	Diabetes mellitus	19	15.08
Temperature (^oC)	≥38.5	108	85.71
	<38.5	18	14.29
Infective foci	Pneumonia	90	71.43
	Catheter-related	20	15.87
	Septicemia	18	14.29
	Endogenous	18	14.29
	Perianal infections	11	8.73
	Skin and soft tissue infections	8	6.35
	Abdominal	7	5.56

Table 4: Cure rate (%) of TGC among three groups of agranulocytosis patients

Group	Patients (N)	Response (n)	Proportion (n/N %)
Monotherapy	15	10	66.67
Initial treatment followed by combination	40	20	50.00
Combination treatment from the start	71	34	47.89

Table 2: Distribution of the pathogens in resistant bacterial infections in concurrent agranulocytosis patients with hematopathies (%)

Pathogen	N	Frequency (%)
Gram-negative bacteria	38	70.37
Stenotrophomonas maltophilia	6	11.11
Klebsiella species	10	18.52
Pseudomonas aeruginosa	6	9.60
Acinetobacter baumannii	2	3.70
Enterobacteriaceae	14	25.93
Gram-positive bacteria	14	25.93
Staphylococcus hominis	4	7.41
S. cohnii	2	3.70
S. haemolyticus	2	3.70
S. epidermidis	3	5.56
Unidentified Gram-positive bacillus	3	5.56
Fungus	2	3.70
Candida tropicalis	2	3.70
Total	54	100.00

though it appeared to be a trend that it was more efficacy when TGC was administrated alone (66.67 % vs. 48.6 %), which is in contrast with recent studies. The possible reason for this finding is the small sample size that caused incorrect results. Importantly, there was a significant difference in response rates between the two combination treatment groups (20/40 {50 %} vs. 34/71 {47.89 %}; p = 0.900), although there appeared to be a trend towards more efficacy of initial treatment, followed by the combination group more so than the combination treatment from the start group.

Table 3: Antimicrobial therapy regimens

Type of antimicrobial therapy	n (%)
TGC monotherapy	15 (11.9)
TGC combination therapy	111(88.1)
Broad-spectrum penicillin +BLI	7(5.56)
Chloromycetin	5(3.96)
Aminoglycosides	8(6.35)
Carbapenem	38(30.2)
Tetracyclines	6(4.7)
Folic acid pathway inhibitor	5(4.0)
Quinolone	14(11.1)
Glycopeptide	3(2.38)
Macrolide	3(2.38)
Nitroimidazole	2(1.59)
Quinolone + ceftazidime	1(0.79)
Quinolone +lincosamide	2(1.59)
Carbapenem +glycopeptide	2(1.59)

Table 5: Toxicity of TGC treatment

Organ (n=126)	Toxicity grade			
	Grade 1(n,%)	***Grade 2(n,%)***	***Grade 3(n,%)***	***Grade 4(n,%)***
Kidney	14 (11.1)	5 (4.0)	3 (2.4)	0
Nausea	24 (19.0)	5 (4.0)	2 (1.6)	0
Vomiting	18 (14.3)	0	0	0
Diarrhea	7 (5.6)	1 (0.79)	0	0
Liver	23 (18.2)	18 (14.3)	3 (2.4)	0
Rash or itching	3 (2.4)	1 (0,79)	0	0
Headache	1 (0.79)	0	1 (0.79)	0
Neuro-Toxicity	0	0	0	0
Phlebitis	0	0	0	0
Sweating	3 (2.4)	0	0	0

Toxicity during TGC therapy

Toxicity data were shown in Table 5. Toxicity induced by TGC therapy occurred in 45 (35.7 %) patients. Grade 3 toxicity occurred in 1 of 9 patients (7.14 %). The main toxicities were nausea with vomiting (14.29 %), nausea without vomiting (11.90 %), diarrhea (6.35 %), and systemic skin rash with itching (3.17 %). All of the adverse side effects resolved after discontinuing TGC. Organ toxicity involving the kidneys and liver was noted in accordance with the drug metabolism process.

DISCUSSION

Even though new and exciting developments have been achieved recently, the main treatment and pathophysiologic characteristics have caused neutropenia in patients with hematopathies. The resulting neutropenia results in morbidity and mortality in patients with hematological disorders. The mortality rates in neutropenic patients with hematopathies and concurrent resistant bacterial infections were very high before the advent of the antibiotic era. The treatment of neutropenic patients changed when empirical antibiotic therapy was introduced; however, the resistance to the antibiotic agents is the main problem that seriously influence the treatment effect on bacterial infections [12]. To solve this problem, it is needed to develop a new broad-spectrum antibacterial agent. TGC was initially approved by the US FDA in June 2005 to indicate the treatment of complex skin, soft tissue, and intra-abdominal infections [13,14]. A clinical retrospective study on the efficiency and safety of the TGC treatment as empirical antibiotic therapy was performed in study. First of all, the clinical features of neutropenic patients with resistant bacterial infections were detected. The results showed that neutropenia usually occurs in patients with hematological malignancies, which is the result of enhanced myelosuppressive chemotherapy. The risk factors for neutropenic adult patients with hematopathies infected with resistant bacteria include intensive chemotherapy, use of central venous catheters, immunosuppression, and diabetic complications. Neutropenia resulting from intensive chemotherapy increases the risk of bacterial infections and repeated central venous catheterization increases the risk of exogenous infections. Immunosuppressive agents can reduce the proliferation and function of immune cells, resulting in weakening of the immune response, and thus increasing the risk of infection. Patients with diabetes mellitus have an underlying metabolic disturbance and significant reduction in disease-resistant ability [19,20]. A fever was the major symptom of infection, accounting for 85.71 % of all cases. Bacteria induce the release of endogenous pyrogens, which can penetrate through blood-brain barrier and cause fever [21]. Clinicians use physical therapy to control the body temperature and sensitive antibiotics to cure infections. Because of the special characteristics of the lung, pneumonia should be avoided in patients with hematopathies. There were some new drugs anti-Gram-positive infections, but the drugs for MDR Gram-negative infections that lead to the occurrence of an increased proportion of bacteremia, and the occurrence of MDR microorganisms were limited [22,23]. In accordance with those results, our study showed that resistant *Escherichia coli* and *Klebsiella pneumonia* bacteremia were the two major pathogens in patients with hematologic malignancies [24]. The cure rate of TGC treatment on the patients with bacteremia was 50.79 %, which is higher than a previous study [25]. It was assumed that long-term use of carbapenem antibiotics before TGC was administered to patients who were not severely ill, which resulted in this finding. In the current study, there was no significant difference in the remission rate between the TGC monotherapy group and the combination therapy group. However, it shown a tendency to increase the effect of using TGC alone, reflecting the wrong sample size.

It is worth noting that there is still no significant difference between the two groups. Although there appeared to be a trend towards more efficacy than combination treatment from the beginning. In this regard, it would be interesting to perform a matched cohort analysis for comparing which kind of combination treatment was suitable for the treatment of MDR/XDRAB neutropenic patients with hematopathies. Inconsistent results have been reported with respect to the combination treatment effect for various MDR/XDRAB infections [26]. The median duration of the group that had good responses to TGC was 2.13 days (range, 0-6 days), indicating that temperature was used as the main parameter to identify patients who were sensitive to TGC. There were some positive outcomes arising from this study. First, the main bacteria were identified which occurred in MDR/XDRAB neutropenic patients with hematopathies. Second, this efficiency is the first comparison between TGC, as initial treatment, followed by combination with other antibiotics and TGC in combination with other antibiotics and treatment.

Limitations

Some limitations existed in this study. First, it was a single-center, retrospective, and underpowered study. Second, it was not a matched cohort analysis, and the variations made our analysis complicated and not precise enough to provide evidence for clinical application. Third, few patients received TGC monotherapy for MDR/XDRAB. However, based on the primary analysis, it is difficult to attribute clinical and microscopic responses to TGC alone or in combination.

CONCLUSION

The results support the view that TGC shows good efficacy for MDR/XDRAB neutropenic patients with hematopathies without any severe side effects. Therefore, clinicians can use TGC as soon as carbapenem antibiotic treatment fails. In addition, due to the lack of high-level evidence of the superiority of combination therapy, TCG combination therapy may not be the main recommendation. Therefore, meticulously designed studies are needed to evaluate the efficacy and safety of combination therapy compared with TGC monotherapy.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. FeifeiChe is the guarantor of integrity of the entire study, study concept, study design, clinical studies, data analysis, statistical analysis, and manuscript preparation. Chunqian Wan is responsible for definition of intellectual content and manuscript editing. Xiaodong Wang is responsible for the literature research and manuscript review. Jiao Chenis is responsible for data acquisition. Juan Huang is responsible for experimental studies.

REFERENCES

1. *Hughes WT, Armstrong D, Bodey GP, Feld R, Mandell GL, Meyers JD, Pizzo PA, Schimpff SC, Shenep JL, Wade JC, et al. From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis 1990; 161: 381-396.*
2. *Maschmeyer G, Heinz WJ, Hertenstein B, Horst HA, Requadt C, Wagner T, Cornely OA, Löffler J, Ruhnke M. IDEA study investigators. Immediate versus deferred empirical antifungal (IDEA) therapy in high-risk patients with febrile neutropenia: a randomized, double-blind, placebo- controlled, multicenter study. Eur J Clin Microbiol Infect Dis 2013; 32(5): 679-689.*
3. *Hu X, Sun A, Zheng J, Zhang T, Qiu H, Gao S, Feng Y, Wu D. Efficacy observation of tigecycline in the treatment of 107 patients with infection due to granulocytopenia. Zhonghua Xue Ye Xue Za Zhi, 2015; 36(7): 583-586.*
4. *Maseda E, Denis SE, Riquelme A, Gilsanz F. Use of tigecycline in critically ill patients with serious nosocomial intra-abdominal infections. Rev ESP Quimioter2013; 26(1):56-63.*
5. *Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). Antimicrob Agents Chemother 1999; 43: 738-744.*
6. *Franklin R, Matthew, Jeff Alder. Performance standards for antimicrobial susceptibility testing; 22nd informational supplement. M100-S22 2012; 32 (3): 2162-2914.*
7. *Chinese Medical Association. The interpretation of anti-infection treatment guideline of neutropenic hematological patients with fever. Chin J Hematol 2012; 33(8): 693-696.*
8. *Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the*

Infectious Diseases Society of America. Clin Infect Dis 2011; 52: 56-93.

9. *Lee DG, Kim SH, Kim SY, Kim CJ, Park WB, Song YG, Choi JH. Evidence-based guidelines for empirical therapy of neutropenic fever in Korea. Korean J Intern Med 2011; 26: 220-252.*
10. *Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, et al. Multidrug-resistant, extensively drug-resistant and pan drug-resistant bacteria, an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268-281.*
11. *Friedman ND, Kaye KS, Stout JE, Mc Garry SA, Trivette SL, Briggs JP, Lamm W, Clark C, Mac Farquhar J, Walton AL, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137: 791-797.*
12. *Wareham DW, Gordon NC, Hornsey M. In vitro activity of teicoplanin combined with colistin versus multidrug-resistant strains of Acinetobacter baumannii. J Antimicrob Chemother2011; 66: 1047-1051.*
13. *Bodmann KF, Heizmann WR, von Eiff C, Petrik C, Löschmann PA, Eckmann C. Therapy of 1,025 severely ill patients with complicated infections in a German multicenter study: Safety profile and efficacy of tigecycline in different treatment modalities. Chemother 2012; 58(4): 282-294.*
14. *Liu JW, Ko WC, Huang CH, Liao CH, Lu CT, Chuang YC, Tsao SM, Chen YS, Liu YC, Chen WY, et al. Agreement assessment of tigecycline susceptibilities determined bythe disk diffusion and broth microdilution methods among commonly encountered resistant bacterial isolates: Results from the Tigecycline in Vitro Surveillance in Taiwan (TIST) study, 2008 to 2010. Antimicrob Agents Chemother 2012; 56 (3): 1414-1417.*
15. *Betts JW, Phee LM, Hornsey M, Woodford N, Wareham DW. In Vitro and In Vivo Activities of Tigecycline-Colistin Combination Therapies against Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother 2014; 58(6): 3541-3546.*
16. *Kanj SS, Whitelaw A, Dowzicky MJ. In vitro activity of tigecycline and comparators against Gram-positive and Gram-negative isolates collected from the Middle East and Africa between 2004 and 2011.Int J Antimicrob Agents 2014; 43(2): 170-178.*
17. *Cattoir V, Isnard C, Cosquer T, Odhiambo A, Bucquet F, Guérin F, Giard JC. Genomic Analysis of Reduced Susceptibility to Tigecycline in Enterococcus faecium. Antimicrob Agents Chemother2015; 59(1): 239-244.*
18. *Shen F, Han Q, Xie D, Fang M, Zeng H, Deng Y. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. Int J Infect Dis 2015;39: 25-33.*
19. *Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics. 2002; 182: 17-23.*
20. *World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza, Brazil, 2013.*
21. *Michail G, Labrou M, Pitiriga V, Manousaka S, Sakellaridis N, Tsakris A, Pournaras S. Activity of tigecycline in combination with colistin, meropenem, rifampin, or gentamicin against KPC-producing Enterobacteriaceae in a murine thigh infection model. Antimicrob Agents Chemother 2013; 57(12): 6028-6033.*
22. *Chen Q, Li X, Zhou H, Jiang Y, Chen Y, Hua X, Yu Y. Decreased susceptibility to tigecycline in acinetobacter baumannii mediated by a mutation in trm encoding SAM-dependent methyltransferase. J Antimicrob Chemother 2014; 69(1): 72-76.*
23. *Wu Y, Hu Z, Xing L, Wang H, Liu H, Guan J, Fu R, Li L, Wang G, Song J, et al. Efficacy of tigecycline in treating severe infections of patients with hematological diseases. National Medical Journal of China 2014; 94(34):2669-2672.*
24. *Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D, di Grazia C, Frassoni F, Bacigalupo A, Viscoli C. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: Reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 2009; 15: 47-53.*
25. *Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R, Arnan M, Marin M, Carratalà J, Gudiol F. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: Clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 2010; 65: 333-341.*
26. *Ortega M, Marco F, Soriano A, Almela M, Martínez JA, Muñoz A, Mensa J. Analysis of 4758 Escherichia coli bacteremia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother 2009; 63: 568-574.*
27. *Hagihara M, Housman ST, Nicolau DP, Kuti JL. In Vitro Pharmacodynamics of Polymyxin B and Tigecycline Alone and in Combination against Carbapenem-Resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2014; 58(2):874-879.*
28. *Batirel A, Balkan II, Karabay O, Agalar C, Akalin S, Alici O, Alp E, Altay FA, Altin N, Arslan F, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. Eur J Clin Microbiol Infect Dis 2014; 33(8):1311-1322.*