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Number of concomitant drugs with thrombocytopenic adverse effects and the extent inflammatory response resolution are risk factors for thrombocytopenia in patients treated with linezolid for more than 14 days

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ABSTRACT

Prolonged treatment with linezolid (LZD) is known to cause thrombocytopenia. However, some patients do not develop thrombocytopenia despite long-term administration of LZD. To determine the risk factors for LZD-associated thrombocytopenia in patients undergoing long-term LZD therapy, we conducted a retrospective cohort study among 212 patients receiving LZD treatment between December 2011 and June 2014 at a tertiary referral university hospital in Nagoya, Japan. Of the 217 patients who received LZD, 37 were treated with LZD for more than 14 days and were enrolled in the study. We compared data on demographic characteristics, underlying disease, microbiology, concomitant drugs, and laboratory tests between the thrombocytopenia group and the non-thrombocytopenia group. Thrombocytopenia was defined as having a platelet count $< 100 \times 10^3/\mu L$ or a $\geq 50\%$ reduction in platelet count compared to baseline. Among the 37 patients who received LZD for more than 14 days, 17 (45.9%) developed thrombocytopenia. Multivariate logistic regression revealed that both the number of concomitant drugs with thrombocytopenic adverse effects (DTADE) (OR = 1.690; 95% CI = 1.037–2.754; $P = 0.035$) and a small decrease in the level of C-reactive protein (CRP) 14 days post-administration (OR = 0.965; 95% CI = 0.939–0.993; $P = 0.013$) were associated with thrombocytopenia during long-term LZD therapy. Therefore, the number of concomitant DTADE and a small decrease in CRP on the 14th day of treatment were key factors for the appearance of LZD-associated thrombocytopenia in patients with long-term LZD therapy. Our findings may be useful for preventing thrombocytopenia in patients treated with LZD for longer than 14 days.

Keywords: linezolid, thrombocytopenia, bacterial infection, MRSA

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Abbreviations:
LZD: linezolid
DTADE: drugs with thrombocytopenic adverse effect
MRSA: methicillin-resistant Staphylococcus aureus
VRE: vancomycin-resistant enterococci
TP: thrombocytopenia
CRP: C-reactive protein
CCr: Creatinine clearance
TDM: therapeutic drug monitoring

INTRODUCTION

Linezolid (LZD) is a broad spectrum oxazolidinone antibiotic used to treat Gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Its mechanism of antimicrobial action is primarily bacteriostatic, and inhibits bacterial protein synthesis by interfering with the fusion of 30S and 50S ribosomal subunits.[1] Because both the intravenous and oral formulations of LZD have nearly 100% bioavailability due to its high water solubility and robust tissue penetration,[2,3] LZD is often used in patients with infectious diseases requiring long-term therapy.

Although, LZD therapy is effective against serious bacterial infections, patients commonly experience significant complications, including bone marrow suppression with consequent anemia and thrombocytopenia; this can lead to discontinuation of LZD therapy. While the exact mechanism of LZD-related bone marrow suppression is still unknown, prolonged treatment duration,[4-9] renal insufficiency,[2-4,10-12] chronic liver disease,[10] baseline platelet count,[13] and daily-per-kg-dose[14,15] have been reported as possible risk factors for LZD-associated thrombocytopenia. These findings indicate that the daily dose of LZD should be adjusted based on body weight and/or renal function. Although this is easy to do in the case of intravenous LZD, unfortunately, the oral formation of this drug is only available as a 600 mg non-scored tablet in Japan, so the options for dose adjustments in outpatient use appear to be quite limited. Moreover, dosage optimization of LZD to avoid dose-dependent toxicity may increase the risk of treatment failure. In order to avoid these risks, therapeutic drug monitoring (TDM) has recently been advocated by some researchers to improve the safe and effective use of LZD.[16] TDM can be a useful tool for adjusting plasma concentrations to obtain optimal pharmacodynamics targets in order to maximize the effectiveness of LZD and avoid adverse effects in patients requiring prolonged treatment. TDM can also be used in critically ill patients or those who are also being treated with P-glycoprotein modulators including omeprazole, clarithromycin and rifampicin.[17,18] Unfortunately, TDM for LZD treatment is currently only available in a limited number of hospitals for research purposes.

On the other hand, some patients undergoing long-term therapy with LZD do not develop thrombocytopenia. However, the factors that allow patients who undergo long-term treatment with LZD to avoid developing thrombocytopenia are unknown; identifying these factors may ensure the safe and effective use of LZD. To address this, we conducted a retrospective cohort survey of patients who received LZD treatment for more than 14 days.

METHODS

Patients and Data collection

We conducted a retrospective cohort study among 212 patients who were treated with LZD at Nagoya University Hospital from December 2011 to June 2014. Of these 212 cases, 37 patients were treated with LZD for more than 14 days (long-term administration) and were enrolled in the study. Patients who developed thrombocytopenia were grouped into the thrombocytopenia (TP) group, and patients who did not develop thrombocytopenia were categorized into the non-thrombocytopenia (NTP) group. LZD was administrated to one patient twice at different doses and intervals; these separate administrations of LZD were counted as two separate cases.

We extracted data from electronic medical records for each patient and analyzed patient characteristics including age, gender, height, body weight, treatment duration, treatment dose, route of drug administration, bacterial species isolated, past-medical history, comorbidity, concomitant drugs, and baseline parameters such as platelet count, C-reactive protein (CRP), and serum creatinine. Laboratory data at day 14 contained data collected at the first follow-up date after day 14 of LZD administration. A small decrease in CRP levels at 14 days post-administration was defined as ≤ 80 % reduction in CRP. Creatinine clearance (CCr) was estimated using the Cockcroft-Gault formula. Baseline platelet count was defined as the mean platelet count at the first day of LZD therapy and the 4 most recent platelet counts data prior to initiation of LZD therapy.

This retrospective cohort study complied with ethical guidelines and was approved by the medical research ethical board at Nagoya University Hospital (2015-0119).

Table 1 Patients' baseline characteristics in this study

Characteristics	
Number of LZD treatment	37
Number of patients	36
Sex (male/female), n	20/17
Age (years), mean±SD	57.4±23.3
Duration of LZD treatment (day), median (range)	17 (15–164)
Place of administration	
Ward	30
ICU	5
Outpatient	2
Patients with thrombocytopenia, n (%)	17 (45.9)

Definition of thrombocytopenia

Thrombocytopenia was defined[4,11,14] as a platelet count of $< 100 \times 10^3/\mu L$ or a ≥ 50% reduction in platelet count from baseline.

Definition of a drug with thrombocytopenic adverse effect (DTADE)

The drug was defined as a DTADE if the package insert listed thrombocytopenia as a potential adverse effect in Japan.

Statistical analysis

Statistical analyses were performed using SPSS (version 24, IBM Japan, Tokyo, Japan)

and Microsoft Excel. Parametric variables were expressed as mean±SD without statement, and compared using Welch's *t*-test. Nonparametric variables were compared using the Chi-square test or Fisher's exact test. We also performed multivariate logistic regression analysis to identify risk factors for thrombocytopenia. Clinically relevant variables that were previously reported to be associated with LZD-associated thrombocytopenia as well as variables with $P < 0.05$ in the univariate analyses were included in the multivariate analysis. A P-value <0.05 (two-tailed) was considered to be statistically significant.

RESULTS

We identified a total of 212 patients who were treated with LZD between December 2011 and June 2014. Of these, 37 cases were treated with LZD for more than 14 days. Because most cases of LZD-associated thrombocytopenia are observed in patients who received LZD for more than 14 days,[9] we included these 37 cases in our study. Thrombocytopenia was found in 17 of 37 cases (45.9%). The baseline characteristics of the 37 patients are described in Table 1. The types of infections and bacteria isolated in the TP and NTP groups are described in Table 2.

Table 2 Comparison of diagnosis and isolated bacteria between TP and NTP groups

	TP group n = 17	NTP group n = 20	*P*-value
Diagnosis			
Osteomyelitis, n (%)	9 (53)	7 (35)	0.331[d]
Artificial device infection[a], n (%)	2 (11)	3 (15)	1.000[d]
Pneumonia, n (%)	3 (17)	2 (10)	1.000[d]
Meningitis, n (%)	1 (6)	2 (10)	0.631[d]
Others, n (%)	2 (12)	6 (30)	0.246[d]
Bacterial strain			
MRSA[b], n (%)	8 (47)	9 (45)	1.000[d]
MR-CoNS[c], n (%)	6 (35)	6 (30)	1.000[d]
Culture negative, n (%)	1 (6)	2 (10)	1.000[d]
Others, n (%)	2 (12)	3 (15)	1.000[d]

[a]without obvious osteomyelitis, [b]MRSA: methicillin-resistant *Staphylococcus aureus*, [c]MR-CoNS: methicillin-resistant coagulase-negative staphylococci, [d]Fisher's exact test

Based on univariate analysis, we found that a small decrease in the level of CRP on day 14 of LZD treatment was a risk factor for LZD-associated thrombocytopenia (Table 3). Body weight, daily-per-kg-dose and CCr that were previously reported as risk factors for thrombocytopenia previously,[2-4,10-12,14,15] were not significantly different between the TP and NTP groups in this study. Interestingly, we found a correlation between the number of concomitant DTADEs and use of trimethoprim-sulfamethoxazole with the incidence of thrombocytopenia (Table 4).

The number of DTADEs (OR = 1.690; 95% CI = 1.037–2.754; P = 0.035) and having only a small decrease in CRP levels at day 14 day of LZD administration (OR = 0.965; 95% CI = 0.939–0.993; P = 0.013) were significantly correlated with LZD-associated thrombocytopenia in the multivariate logistic regression analysis (Table 5).

Table 3 Characteristics and clinical data of patients

	TP group n = 17	NTP group n = 20	*P*-value
Age (years)	53.5±23.9	58.5±23.5	0.549[a]
Height (cm)	151.8±20.6	150.8±24.7	0.905[a]
Body weight (kg)	55.1±20.8	53.4±24.5	0.818[a]
Duration of LZD treatment (day), median (range)	16.0 (15–30)	17.5 (15–164)	0.124[a]
Daily-per kg-dose (mg/kg/day)	22.1±5.3	22.2±6.0	0.961[a]
Serum Creatinine (mg/dL)	1.14±1.83	0.99±0.94	0.774[a]
CCr (mL/min)	86.3±38.6	92.5±56.7	0.708[a]
Baseline platelet ($\times 10^3/\mu L$)	235.35±87.3	232.8±71.3	0.924[a]
CRP (mg/dL)			
before administration	4.69±7.21	8.42±6.83	0.132[a]
14 days post-administration	2.23±3.54	1.15±1.29	0.278[a]
Decrease rate of CRP at Day14 (%)	42±47	76±32	0.034[a]
Small decrease rate of CRP, n (%)	13 (76)	6 (30)	0.008[b]
Route of LZD administration			0.244[b]
Intravenous, n (%)	1 (6)	5 (25)	
Intravenous + Oral, n (%)	5 (29)	7 (35)	
Oral, n (%)	11 (65)	8 (40)	
Surgery, n (%)	11 (65)	14 (70)	1.000[b]
Baseline disease			
Chronic inflammatory disease, n (%)	2 (12)	5 (25)	0.416[b]
Diabetes mellitus, n (%)	4 (24)	7 (35)	0.495[b]
Chronic kidney disease, n (%)	3 (18)	5 (25)	0.701[b]
Hypertension, n (%)	6 (35)	6 (30)	1.000[b]
Hematological disease, n (%)	0 (0)	2 (10)	0.489[b]
Vascular disease, n (%)	9 (53)	15 (75)	0.188[b]
Respiratory disease, n (%)	5 (29)	10 (50)	0.315[b]
Neoplasm, n (%)	4 (24)	9 (45)	0.173[b]

[a]Welch's *t*-test, [b]Fisher's exact test

Table 4 Summary of concomitant drugs in in long-term administration group

	TP group n = 17	NTP group n = 20	*P*-value
Number of concomitant drugs	7.3±4.3	6.1±3.5	0.368[b]
Number of concomitant DTADEs	4.6±2.3	3.0±1.7	0.023[b]
Concomitant drugs			
Antimicrobial drugs, n (%)	8 (47)	6 (30)	0.328[c]
Antibiotics, n (%)	7(41)	5 (25)	0.482[c]
Trimethoprim-sulfamethoxazole, n (%)	4 (24)	0 (0)	0.036[c]
Rifampicin, n (%)	3 (18)	0 (0)	0.088[c]
Antacids, n (%)	10 (59)	14 (70)	0.512[c]
Proton pump inhibitor, n (%)	8 (47)	12 (60)	0.517[c]
Histamine H_2-receptor antagonist, n (%)	2 (12)	2 (10)	1.000[c]
Antipyretic analgesics, n (%)	11 (65)	7 (35)	0.053[c]
NSAID[a], n (%)	8 (47)	6 (30)	0.328[c]
Antihypertensive, n (%)	5 (29)	10 (50)	0.315[c]

[a]Non-Steroidal Anti-Inflammatory Drug, [b]Welch's *t*-test, [c]Fisher's exact test

Table 5 Multivariate logistic regression analysis of risk factors associated with LZD-induced thrombocytopenia

Factors	Odds ratio (95% CI)	*P*-value
Number of DTADEs	1.690 (1.037–2.754)	0.035
Decrease rate of CRP at Day14 (%)	0.965 (0.939–0.993)	0.013
CCr (mL/min)	1.010 (1.000–1.021)	0.062
Baseline platelet ($\times 10^3/\mu L$)	1.003 (0.990–1.016)	0.669
Daily-per-kg-dose	1.185 (0.980–1.435)	0.080

In this multivariate logistic regression analysis, daily-per-kg-dose, CCr, and baseline platelet were entered forcedly because they were previously reported as the risk factors for TP. Other variables with *P*-value less than 0.05 in univariate analyses were entered by backward stepwise elimination methods with inclusion of *P*-value less than 0.05.

DISCUSSION

Linezolid is highly effective for treating Gram-positive bacterial infections including MRSA and VRE.[19,20] One of the advantages of LZD is high oral bioavailability,[2,3] which enables patients to switch from intravenous to oral treatment early in therapy. Therefore, LZD is a reasonable choice for patients with complex soft tissue infections and osteomyelitis who require long-term therapy, because of its ability to penetrate bone tissue. On the other hand, one of the major adverse effects of LZD therapy is bone marrow suppression, particularly thrombocytopenia. Periodic monitoring of hematological parameters is recommended for patients receiving LZD therapy, because development of thrombocytopenia may require discontinuation of LZD.[1] While long-term administration has been reported to be a risk factor for LZD-associated thrombocytopenia,[4-9] data on patients who have received prolonged LZD treatment are insufficient. In this study, we defined thrombocytopenia as a platelet count $< 100 \times 10^3/\mu L$ based on the previous studies of LZD-associated thrombocytopenia[4,11]; this enabled us to compare our findings to previous studies. Since large reductions in platelet counts such as $300 \times 10^3/\mu L$ to $120 \times 10^3/\mu L$ are excluded from this definition of thrombocytopenia (platelet count $< 100 \times 10^3/\mu L$), we also defined thrombocytopenia as a $\geq 50\%$ reduction in platelet count from baseline. A similar definition was also used in to another prior study.[14] Based on these criteria, thrombocytopenia was observed in 45.9% of patients who were treated with LZD for more than 14 days in our study. We identified two factors that a showed significant relationship with the incidence of LZD-associated thrombocytopenia: the number of concomitant drugs that have a thrombocytopenic adverse effect and having only a small decrease in CRP levels at day 14 of LZD administration.

A small decrease in CRP levels is correlated with a high incidence of LZD-associated thrombocytopenia, indicating that the initial resolution of inflammatory response has an influence on the occurrence of thrombocytopenia. In addition to the appropriate antimicrobial chemotherapy, early intervention such as source-control procedures are important for patients receiving LZD for early resolution of inflammation to prevent drug-induced thrombocytopenia.

Moreover, drug-induced thrombocytopenia is suspected in patients with acute thrombocytopenia unexplained by other causes. However, identifying the cause of drug-induced thrombocytopenia is difficult, particularly in patients taking multiple medications where acute thrombocytopenia is a potential risk. At least 1,468 medicines have been shown to cause thrombocytopenia as an adverse effect,[21] suggesting that the frequency of drug-induced thrombocytopenia is even greater than prior estimates. Since the use of concomitant DTADE with LZD can result in serious risk for thrombocytopenia, clinicians managing patients receiving LZD therapy should carefully evaluate and discontinue unnecessary concomitant drugs that have potential to induce

thrombocytopenia. While the mechanism of LZD-induced thrombocytopenia is unknown, two possible mechanisms been proposed: drug-induced antibody destruction of specific hematopoietic cells and direct toxicity to mitochondria leading to the inhibition of protein synthesis.[22] Therefore, we speculate that DTADEs have an additive suppressive effect on platelet production in LZD-induced thrombocytopenia.

Although renal insufficiency and higher daily-per-kg-doses of LZD have also been reported as risk factors for LZD-associated thrombocytopenia,[2-4,10-12,14,15] we did not find any significant relationship between these factors and the incidence of LZD-associated thrombocytopenia in our study. This discrepancy may be due to differences in management policies at our study site as well as study design. The infection control team was involved in overseeing treatment in most of the cases in our study when LZD was administered. It is likely that patients at risk for LZD-associated thrombocytopenia such as renal insufficiency and low baseline platelet count were not treated with LZD for Gram-positive bacterial infections. Moreover, we focused on the additional risks for LZD-associated thrombocytopenia in patients undergoing long-term LZD therapy; only patients treated with LZD for more than 14 days were enrolled in our study, which differed from previous studies.

There are some limitations to the present study. First, this is a retrospective study conducted in a single hospital which could introduce patient selection bias, limiting the generalizability of our results. A multi-center study with more cases would be required for adequate statistical power for the analysis. Second, we did not investigate the serum concentration of LZD; therefore, the relationship between the pharmacokinetics/ pharmacodynamics and adverse effects are inconclusive. Third, the number of cases in the present study was small.

In conclusions, we found that both the number of DTADEs and a delayed reduction in CRP level are significant risk factors for LZD-associated thrombocytopenia in patients undergoing long-term LZD therapy. Identification of these risk factors could be valuable in preventing development of the LZD-associated thrombocytopenia by allowing clinicians to take appropriate interventions such as reconsideration of concomitant drugs and/or source infection control.

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FOOTNOTE

This manuscript has been edited for English language, grammar, punctuation and spelling by Enago (www.enago.jp).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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