Exploring the impact of baseline platelet count on linezolid-induced thrombocytopenia: a retrospective single-center observation study

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Abstract

Background Patients treated with linezolid (LZD) often develop thrombocytopenia, and risk factors for LZD-induced thrombocytopenia (LIT) have been identified in previous studies.

Aim The relationship between the development of LIT and baseline platelet counts varies according to different reports. Thus, this study aimed to clearly define this relationship.

Methods: We analyzed patients who received LZD at Hokkaido University Hospital from September 2008 to March 2023. We collected data on patient characteristics and platelet counts at baseline and during LZD therapy from electronic medical records. LIT was defined as a decrease in platelet count by 30% or more from baseline, or a platelet level <100,000/μL.

Results: A total of 295 patients who received LZD were included in this study; 34.9% of them developed LIT. Focusing on the early onset of LIT (LIT ≤5 days), baseline platelet counts were significantly lower in those who developed LIT early. Specifically, a baseline platelet count of less than 150,000/μL was identified as a risk factor for early LIT development (LIT ≤5 days). Conversely, it was also noted that 24.7% of patients with baseline platelets ≥150,000/μL developed LIT early during LZD treatment.

Conclusions: Our findings suggest that vigilant monitoring of platelet counts by clinical pharmacists is essential in the early stages of LZD treatment, regardless of baseline platelet levels.

Keywords

linezolid, thrombocytopenia, adverse drug effects, platelet count

Impact statements

- The baseline platelet count is not a risk factor for LIT when analyzed over the entire duration of LZD treatment, however, the baseline platelet count of less than 150,000/μL has been identified as a risk factor for the early development of LIT (≤5 days).
- Clinical pharmacists could play a crucial role in ensuring safer and more effective treatment with LZD by carefully monitoring platelet counts during the initial phase of LZD administration.

1 INTRODUCTION

Thrombocytopenia is a common side effect of linezolid (LZD) treatment for gram-positive bacterial infections, such as methicillin-resistant *Staphylococcus aureus*. LZD-induced thrombocytopenia (LIT) affects 25–60% of patients treated with LZD and frequently necessitates treatment interruption [1-5]. We previously reported risk factors for LIT using extensive Japanese datasets, identifying prolonged LZD therapy, body weight <45 kg, and renal dysfunction as significant factors. Decision tree analysis further highlighted that the highest risk scenario involved LZD therapy lasting ≥14 days and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 [6]. Given the narrow therapeutic window of LZD—where inadequate exposure can lead to therapy failure, while excessive dosing can cause LIT—therapeutic drug monitoring (TDM) is recommended for patients presenting these risk factors. TDM for LZD has been advocated in some studies [7,8], with incidents of LIT occurring in approximately 50% of patients whose area under the 24-hour concentration-time curve (AUC) ≥280 μg×h/mL [9]. Optimal therapeutic responses with minimal side effects were observed when LZD trough concentrations ranged between 2 and 8 mg/L [10,11], and 90.5% of patients with renal impairment in the TDM cohort required dosage adjustments to achieve target trough concentrations [12]. Additionally, patients who later experienced drug-related adverse events had significantly higher plasma LZD concentrations during the initial assessment in the first week of therapy [13]. Unlike LZD, the dosage of vancomycin—a similar anti-MRSA

medication—is typically managed with TDM according to current guidelines. However, TDM for LZD has not yet been widely implemented in clinical practice. Therefore, establishing the need for TDM or dosage adjustments based on early platelet count fluctuations following the initiation of LZD therapy could be crucial for clinical management.

Base platelet count is also considered a potential factor in deciding whether to perform TDM. However, our previous comparisons of patient characteristics between those with LIT and those without did not reveal any differences in baseline platelet values [6]. This finding aligns with several other studies [14-19]. Conversely, a recent meta-analysis by Zhang et al. indicated that baseline platelet values were associated with an increased risk of LIT [20].

2. Aim

In this study, we aimed to explore the relationship between baseline platelet count, the platelet count prior to LZD administration, and the development of LIT by examining patients' platelet counts over time during LZD treatment. To effectively analyze platelet count trends, continuous data on platelet counts for each patient throughout the LZD treatment period is essential. Therefore, we decided to conduct our study using medical record data from Hokkaido University Hospital.

3. Ethics approval

This study was conducted in accordance with the Guidelines for Human Care. This study was approved by the Institutional Review Board of the Hokkaido University Hospital for Clinical Research (no. 023-0170).

4 Method

4.1 Study design

A single-center, retrospective observational study was conducted at Hokkaido University Hospital (no. 023-0170).

4.2 Subjects

All patients who had been administered LZD at a dose of 1200 mg daily, either intravenously or orally, at Hokkaido University Hospital from September 2008 to March 2023, were enrolled. LZD was identified by the Anatomical Therapeutic Chemical (ATC) system code No. J01XX08. Patients were excluded if they met any of the following criteria: (1) age <18 years, (2) LZD therapy duration <3 days, (3) baseline platelet values <100,000/μL, (4) the number of platelet count data during LZD therapy <3, (5) the interval of platelet count test ≥4 days, and (6) other missing values.

4.3 Definition of linezolid-induced thrombocytopenia

LIT was defined as a decrease in platelets of 30% or more from baseline or a platelet level of <100,000/μL [6].

4.4 Data collection

Data were retrospectively extracted from medical records, including LZD administration route and therapy duration, patient age, body weight, and baseline serum creatinine (Scr) level. Among patients who developed LIT, the duration from the start of LZD administration to the onset of LIT was assessed. Platelet counts at baseline and during LZD therapy were also extracted. Baseline laboratory data were taken from the day LZD therapy started, or within a maximum of 14 days prior. The eGFR was calculated using the formula: $eGFR = 194 \times Scr^{-1.094} \times Age^{-0.287}$ (for female, × 0.739) [21]. The percentage plate decrease was calculated as 100% × (baseline platelet count–platelet count of the day) / baseline platelet count. A negative value indicates an increase in platelet counts after starting LZD therapy. The initial rate of decrease in platelet count was first calculated by comparing the platelet count on the third day of administration with the baseline. However, since the maximum acceptable interval between tests was up to 3 days, and some patients were not tested on the third day, the initial rate of decrease was calculated using data from the second day if third-day data were unavailable, or from the fourth day if second-day data were also not available.

4.5 Statistical analysis

The characteristics of patients, as described in the data collection section, were used for analysis. Continuous variables were presented as medians with their interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Categorical variables were presented as counts and percentages and evaluated using Pearson's chi-squared test. All statistical analyses were performed using JMP version 16 (SAS Institute Inc., Cary, NC, USA). A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

5 Result

5.1 Characteristics of the study population

Of the 982 patients treated with LZD from September 2008 to March 2023, 295 were enrolled in this study (Figure 1). LIT occurred in 34.9% (n=103) of these patients. The results of the univariate analysis of patient characteristics are presented in Table 1. Significant differences between patients with LIT and those without were observed in LZD treatment duration, eGFR, and the percentage of platelet decrease from day 2 to 4.

5.2 Patient characteristics with LIT

Among the patients who developed LIT (n=103), we analyzed two subgroups: those in whom LIT occurred within 5 days of initiating LZD treatment and those in whom it occurred later.

126 The analysis revealed a significant difference in baseline platelet counts, which were notably
127 lower in the early-onset LIT group compared to the later-onset group (Table 2). This distinction
128 in baseline platelet counts was not observed when analyzed over the entire treatment period.
129
130 **5.3 Patient with or without Baseline platelet count <150,000/μL**
131 Patients were divided into two groups according to their base platelet counts (≥150,000/μL or
132 less than 150,000/μL). The incidence of LIT in patients with base platelet count <150,000/μL
133 was higher than in those patients with ≥150,000/μL (46.9% vs. 31.6%). The rate of platelet
134 count reduction in the early days of LZD treatment (days 2–4) was significant in the LIT group,
135 irrespective of baseline platelet count. Furthermore, among patients with baseline platelet
136 counts ≥150,000/μL, those in the LIT group exhibited significantly impaired renal function,
137 with nearly twice as many patients having an eGFR <30 mL/min/1.73 m^2 compared to the non-
138 LIT group (Tables 3 and 4).
139
140 **6 Discussion**
141 **6.1 Statement of key findings**
142 The present study focused on baseline platelet counts and their changes during LZD
143 administration. To date, only a few studies have examined changes in platelet counts over time
144 during LZD treatment, and these studies typically involve a limited number of cases [22–24].

In this study, 295 patients were included and the overall incidence of LIT was 34.9%, which aligns with previous research [25–27]. A baseline platelet counts <150,000/μL was identified as a risk factor LIT occurring ≤5 days. Conversely, 24.7% of patients with a baseline platelet count ≥150,000/μL also developed early LIT. Regardless of baseline platelet counts, careful monitoring of platelet levels from the early stages of LZD administration is considered a key point for avoiding the occurrence of LIT as much as possible while administering LZD.

6.2 Interpretation

A comparison of patient backgrounds between the LIT and non-LIT groups revealed no significant differences in baseline platelet counts, corroborating our previous findings. Additionally, the duration of LZD treatment was significantly longer in the LIT group, and renal function, as measured by the eGFR, was significantly poorer in the LIT group, consistent with prior studies. On the other hand, the evaluation of platelet counts over time during LZD treatment, an aspect not adequately addressed in previous research, indicated that platelet counts during the early phase of treatment, specifically on days 2-4, were significantly reduced from baseline levels. Furthermore, the rate of decrease in platelet count from baseline was significantly greater in the LIT group (Table 1).

In this study, we focused on patients who developed LIT (n=103) and compared their backgrounds by dividing them into two groups: those who developed LIT within 5 days of

164 starting LZD treatment and those who developed LIT later. The results indicated a significant
165 difference in baseline platelet counts, which were notably lower in the early LIT group (Table
166 2), although these differences were not evident when analyzed over the entire treatment period.
167 Choi et al. reported that baseline platelet counts below 150,000/μL were associated with early
168 LIT development [28], a finding that our results corroborate. Consequently, we categorized
169 LZD-treated patients by baseline platelet count of 150,000/μL and further segmented them into
170 LIT and non-LIT groups for comparison (Tables 3 and 4). The incidence of LIT in patients with
171 baseline platelet counts <150,000/μL was 46.9%, compared to 31.6% in those with counts
172 ≥150,000/μL. Nonetheless, more than 50.0% of patients with baseline counts less than
173 150,000/μL did not develop LIT. Specifically, the proportion of patients with baseline counts
174 <150,000/μL who developed early LIT was almost double that of patients with counts
175 ≥150,000/μL (46.7% vs. 24.7%). These results suggest that while baseline platelet count is a
176 risk factor for early LIT, it is not a significant risk factor when analyzed over the entire treatment
177 period, which explains the variance in findings across different reports.
178 Examining the rate of platelet count reduction in the early days of LZD treatment (days 2–4),
179 it was evident that the reduction was significantly greater in the LIT group, regardless of
180 baseline platelet count. Furthermore, even among patients who began LZD treatment with a
181 baseline platelet count ≥150,000/μL, maintained relatively stable platelet levels, 24.7% of those
182 who expressed LIT developed the condition within the first 5 days of treatment. This

183 underscores the importance of monitoring platelet counts early in the treatment period,
184 particularly on days 2–4.

185 On the other hand, among patients with baseline platelet counts ≥150,000/μL, renal function
186 was significantly poorer in the LIT group. Additionally, 61.1% (22/36) of patients who
187 experienced a decrease of ≥15% (half the decrease defined for LIT) in platelet count on days
188 2–4 of LZD treatment expressed LIT. The incidence of LIT was approximately twice as high
189 in patients with an eGFR <30 mL/min/1.73 m² compared to those with an eGFR ≥30
190 mL/min/1.73 m². This indicates that special caution is necessary in patients with an eGFR <30
191 mL/min/1.73 m², even if their baseline platelet count is ≥150,000/μL. TDM should be
192 implemented, and dosage adjustments considered, especially if long-term LZD administration
193 is planned.

194 Furthermore, the long-term administration of LZD, identified as a risk factor in this study, has
195 been widely reported to increase the risk of LZD-induced thrombocytopenia (LIT) as the
196 duration of treatment extends beyond 14 days. The background comparison between the LIT
197 and non-LIT groups revealed that the LIT group underwent significantly longer treatment
198 periods (Table 1). Among the non-LIT patients, 42.2% (n=81) had platelet counts below their
199 baseline at the end of LZD treatment, with a median decrease of 15.3%. In our cohort, the
200 longest treatment duration was 38 days; however, bone infections often require much more
201 prolonged therapy. Thirot et al.'s study reported that some patients were treated with LZD for

up to 121 days, approximately four months [29]. Most patients experienced a decrease in platelet count due to LZD treatment, indicating that those with bone infections necessitating extended LZD therapy are likely to be diagnosed with LIT eventually. Thirot et al. also noted that patients treated for over 80 days without developing thrombocytopenia had LZD trough concentrations within the therapeutic range of 2–8 mg/L [29]. This suggests that TDM for patients undergoing long-term LZD therapy could enable continuous treatment without interruption due to adverse effects, as long as dosages are maintained within the therapeutic range.

6.3 Strengths and weaknesses

This single-center retrospective observational study has certain weak points. Although the number of patients was limited, it was more adequate than in previous reports, as it included evaluations of platelet counts at multiple points during the treatment period for each patient. Specifically, we focused on patients who had their platelet counts tested every 3 days or more frequently during the LZD administration period, which is a key strength of this study. An association between plasma levels of LZD and LIT has been reported; however, because LZD plasma levels are generally not measured, we did not have access to this data, which is also a weak point of this study.

6.4 Further research

Since this study was conducted at a single center, research involving a larger and more diverse patient population across multiple centers is needed. Additionally, this was a retrospective study, and we were unable to verify missing data, including LZD plasma concentrations. Therefore, prospective studies that include measurements of LZD plasma levels are required as the next step.

7 Conclusion

The vigilant monitoring of platelet counts by clinical pharmacists early in LZD treatment is essential regardless of baseline levels. Additionally, patients with impaired renal function (eGFR <30 mL/min/1.73 m^2) are at a higher risk of developing LIT, even if their platelet counts do not decrease in the early stages of treatment. Furthermore, as long-term administration is considered a risk factor for LIT, patients in this high-risk group and those anticipating prolonged treatment may improve their chances of continuing LZD without developing LIT if TDM is performed once LZD concentrations stabilize.

Author contributions

All the authors contributed to the conception and design of this study. YI and YT performed the material preparation, data collection, and analysis. The first draft of the manuscript was written by YI, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final version of this manuscript.

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Conflicts of interest

All authors declared no competing interests for this work.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Comparison of patient characteristics between those with LIT and those without (n=295)

	With LIT (n=103)	Without LIT (n=192)	*p* value
Age (year), median (Q1–Q3)	66.0 (57.0–76.0)	63.0 (48.0–74.0)	0.09
Body weight (kg), median (Q1–Q3)	58.6 (50.7–66.0)	59.8 (50.8–69.0)	0.55
Administration period of LZD (days), median (Q1–Q3)	12.0 (9.0–15.0)	8.0 (5.3–11.0)	<0.01*
Base platelet count($\times 10^4/\mu L$), median (Q1–Q3)	24.3 (14.1–31.7)	22.5 (17.1–28.9)	0.84
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	44.4 (22.4–75.0)	63.7 (35.1–90.1)	<0.01*
Percent of plate decrease of day 2-4 (%), median (Q1–Q3)	4.8 (-8.4–19.1)	-6.9 (-25.6–3.3)	<0.01*

LIT, linezolid-induced thrombocytopenia; LZD, linezolid; eGFR, estimated glomerular filtration rate; Q1, first quartile; Q3, third quartile

*significantly different (p <0.05)

355 Table 2. Comparison of patient characteristics with LIT between those with LIT development
356 ≤5 days and those without (n=103)

	With LIT (n=103)		
	the duration of LIT development ≤5 days (n=32)	the duration of LIT development >5 days (n=71)	*p* value
Age (year), median (Q1–Q3)	67.5 (58.3–76.8)	65.0 (56.0–75.0)	0.51
Body weight (kg), median (Q1–Q3)	57.2 (49.9–65.2)	60.8 (51.5–67.9)	0.38
Administration period of LZD (days), median (Q1–Q3)	8.0 (6.0–11.0)	13.0 (11.0–17.0)	<0.01*
Base platelet ($\times 10^4/\mu L$), median (Q1–Q3)	16.1 (11.4–28.3)	25.0 (16.3–32.9)	0.02*
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	37.6 (22.5–57.9)	49.3 (21.1–82.0)	0.21
Percent of plate decrease of day 2-4 (%), median (Q1–Q3)	25.5 (18.1–38.6)	-1.7 (-12.5–6.9)	<0.01*
LIT development day (day), median (Q1–Q3)	3 (2–4)	9 (7–11)	<0.01*

357 LIT, linezolid-induced thrombocytopenia; LZD, linezolid; eGFR, estimated glomerular
358 filtration rate; Q1, first quartile; Q3, third quartile
359 *significantly different (p <0.05)
360
361

Table 3. Comparison of patient characteristics with base platelet <150,000/μL between those with LIT and those without (n=64)

	Base platelet <150,000/μL (n=64)		
	With LIT (n=30)	Without LIT (n=34)	*p* value
Age (year), median (Q1–Q3)	63.5 (56.0–75.3)	64.5 (44.8–72.5)	0.44
Body weight (kg), median (Q1–Q3)	63.3 (54.1–68.0)	60.5 (49.8–67.4)	0.62
Administration period of LZD (days), median (Q1–Q3)	9.0 (8.0–12.0)	7.0 (5.0–10.0)	0.03*
Base platelet ($\times 10^4$/μL), median (Q1–Q3)	12.3 (11.2–13.9)	12.9 (11.5–13.8)	0.53
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	46.4 (23.6–60.7)	44.5 (29.7–92.4)	0.62
eGFR <30 (mL/min/1.73 m^2), n (%)	10 (33.3)	9 (26.5)	0.55
Percent of plate decrease of day 2-4 (%), median (Q1–Q3)	10.8 (-1.6–18.1)	-25.5 (-50.2– -2.3)	<0.01*
The duration of LIT development ≤5 days, n (%)	14 (46.7)		

LIT, linezolid-induced thrombocytopenia; LZD, linezolid; eGFR, estimated glomerular filtration rate; Q1, first quartile; Q3, third quartile

*significantly different (p <0.05)

Table 4. Comparison of patient characteristics with base platelet ≥150,000/μL between those with LIT and those without (n=231)

	Base platelet ≥150,000/μL (n=231)		
	With LIT (n=73)	Without LIT (n=158)	*p* value
Age (year), median (Q1–Q3)	66.0 (57.0–76.0)	62.0 (48.0–74.3)	0.11
Body weight (kg), median (Q1–Q3)	56.2 (50.5–64.7)	59.2 (50.8–70.0)	0.27
Administration period of LZD (days), median (Q1–Q3)	13.0 (10.0–17.0)	8.0 (6.0–11.0)	<0.01*
Base platelet ($\times 10^4$/μL), median (Q1–Q3)	28.1 (22.8–35.6)	24.5 (19.0–30.2)	<0.01*
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	44.4 (18.9–78.5)	68.0 (38.9–89.5)	<0.01*
eGFR <30 (mL/min/1.73 m^2), n (%)	24 (32.9)	28 (17.7)	0.01*
Percent of plate decrease of day 2-4 (%), median (Q1–Q3)	0.2 (-10.2–20.0)	-4.8 (-21.6–3.8)	<0.01*
Percent of plate decrease of day 2-4 >15%, n (%)	22 (30.1)	14 (8.9)	<0.01*
The duration of LIT development ≤5 days, n (%)	18 (24.7)		

LIT, linezolid-induced thrombocytopenia; LZD, linezolid; eGFR, estimated glomerular filtration rate; Q1, first quartile; Q3, third quartile

*significantly different (p <0.05)

376 **Figure legends**

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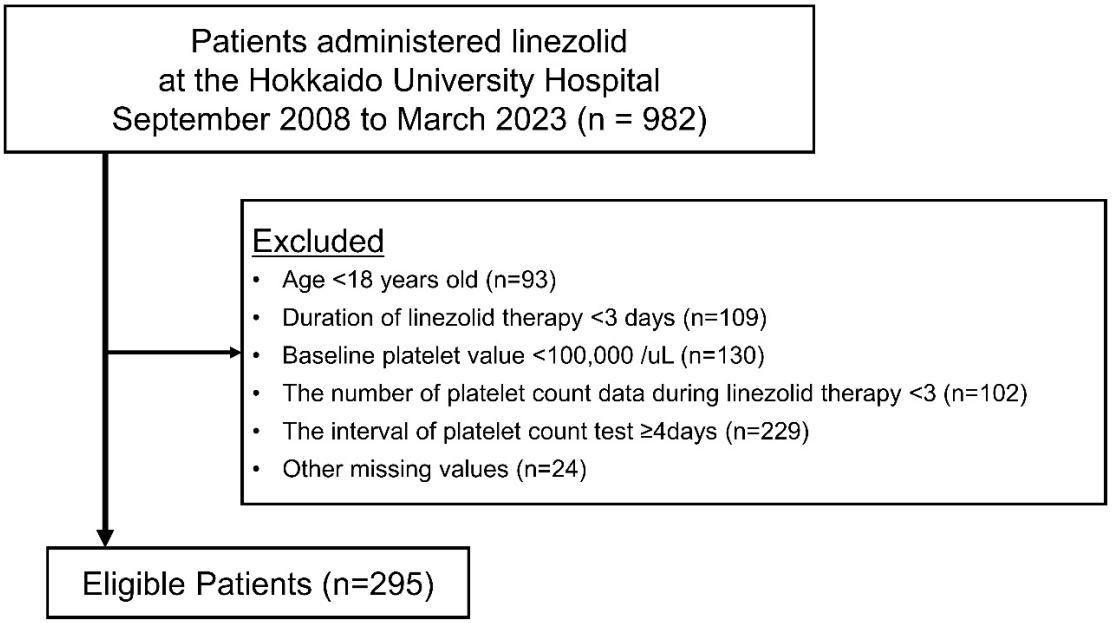

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379 **Figure 1. Patient selection flowchart.**

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