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ORIGINAL RESEARCH

Rapid Onset and Recovery Linezolid-Induced Thrombocytopenia: A Large-Sample, Single-Center Retrospective Cohort Study

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Introduction: Thrombocytopenia is a common and potentially severe adverse effect of linezolid, but the time to onset during treatment has varied substantially across studies. Moreover, the time to recovery after linezolid withdrawal has not been examined in a larger patient sample.

Objective: The first objective of this study was to measure the mean time to linezolid-induced thrombocytopenia (LIT) and the second was to measure the mean time to recovery after linezolid discontinuation.

Methods: A retrospective observational cohort study was conducted between January 2017 and December 2022 at Dammam Medical Complex using the medical records of hospitalized adults with normal baseline platelet counts receiving intravenous linezolid for a minimum of 48 hours. All patients included in the analyses received daily platelet count monitoring for up to 14 days after linezolid initiation and 14 days after discontinuation. Thrombocytopenia was defined as a drop in platelet count to $<150 \times 10^9$/L or <50% of baseline within 14 days. The dose duration–risk relationship and recovery rate were analyzed by constructing Kaplan–Meier survival curves.

Results: In total, 334 patients met study inclusion criteria. The mean time to develop thrombocytopenia after starting linezolid was five days, and the mean time of recovery was also 5 days. The cumulative risk of thrombocytopenia reached 100% by day six of therapy, and cumulative recovery reached 100% by day six after linezolid withdrawal, with half of the study population recovering by day four.

Conclusion: Thrombocytopenia can develop rapidly during linezolid treatment, but recovery after discontinuation is also rapid. Rapid thrombocytopenia is a common adverse effect of linezolid that must be considered prior to prescription, and routine monitoring of platelet count is recommended so that linezolid treatment can be discontinued, if thrombocytopenia occurs.

Keywords: linezolid, thrombocytopenia, induced, recovery

Introduction

Linezolid is an oxazolidinone antibiotic used in many countries for the treatment of infections by drug-resistant pathogens such as vancomycin-resistant enterococci and methicillin resistant *Staphylococcus aureus*.[1] Although it has good coverage for gram-positive bacteria, it may cause serious adverse effects such as serotonin syndrome, peripheral neuropathy, and myelosuppression, potentially resulting in anemia, pancytopenia, leukopenia, and (or) thrombocytopenia.[2] Proposed mechanisms for linezolid-induced thrombocytopenia (LIT) include suppression of platelet release from mature megakaryocytes, oxidative damage to circulating platelets, and immune-mediated platelet destruction.[3] Therefore, platelet counts should be monitored carefully for patients with preexisting thrombocytopenia, at increased risk of bleeding, receiving other medications that may decrease platelet count, or receiving linezolid therapy for 14 days or more.[1,2]

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Thrombocytopenia is considered among the most frequent adverse effects of linezolid, but incidence has varied markedly across studies.[2,3] For example, LIT has ranged from 0.3% to 10% across Phase 3 clinical trials (average of 2.4%),[2] while post-marketing studies have reported substantially higher incidence (15%–50%).[3] The time to LIT has also varied. The United States Food and Drug Administration label states that LIT develops primarily after 14 days or more of daily oral or intravenous (IV) therapy.[4] The manufacturer has also argued that LIT generally occurs only after more than 14 days of treatment and that platelet counts usually return to normal during follow-up.[2] A post-hoc study of clinical trial data similarly concluded that LIT risk increased after about two weeks, reaching 4.1% compared to an average incidence of 2.9% for all treatment durations.[5] However, more recent studies have reported LIT onset earlier than 14 days after initiation, including a retrospective observational cohort study reporting 50% incidence within 14 days and a prospective observational study reporting LIT in about 50% of patients within 11 days.[3] Furthermore, LIT onset has been reported in as little as 5 days.[3]

Thrombocytopenia can lead to life-threatening complications. One study assessing the frequency and clinical characteristics of LIT found gastrointestinal bleeding (GIB) among patients with <100,00 platelet/mm,[3] and some of these patients required platelet transfusion,[1] consistent with previous studies on thrombocytopenia.[3,6,7] Additionally, a study at a large teaching hospital in 2002 evaluating indications, outcomes, and adverse events of linezolid during the first 12 months of approval reported that two of ten cases developing LIT ended in death.[8]

Given these uncertainties in LIT incidence, time to onset, time to recovery, and frequency of severe complications, we conducted a large-scale single-center retrospective study of patients receiving linezolid treatment with daily monitoring of platelet count. Thus, the study findings may diminish the existed knowledge gab related to LIT and help clinicians identify thrombocytopenia as a potential adverse effect of linezolid at early time treatment.

Methods

This retrospective cohort study enrolled patients admitted to Dammam Medical Complex hospital inpatient wards between January 2017 and December 2022 and developing thrombocytopenia within 14 days while receiving IV linezolid. Thrombocytopenia was defined as a drop in platelet count to $<150 \times 10^9$ /L or <50% of baseline after starting linezolid. A list of inclusion and exclusion criteria were established to minimize selection bias (Table 1).

The initial screening ensured that if the included patients received routine anticoagulants (ie, heparin or enoxaparin) for venous thromboembolism prophylaxis, no reported heparin-induced thrombocytopenia was observed to control this adverse event as a confounder. Another controlled confounder was sepsis. If thrombocytopenia is induced by sepsis and not by linezolid, sepsis-induced thrombocytopenia would improve upon treatment with antibiotics, including linezolid, and the study population had normal platelets count prior to linezolid initiation.

The Dammam Medical Complex (DMC) electronic system MedicaCloud was used to identify patients admitted from January 2017 to December 2022 and receiving IV linezolid as inpatients (n = 1800). Of these, 334 met all inclusion and exclusion criteria. An online sample size calculator (https://www.calculator.net/sample-size-calculator.html?type=1&cl=95&ci=5&pp=50&ps=1800&x=86&y=13)) indicated that a group of 317 patients would be needed to yield time-to-event distributions including population mean onset and reversal of LIT estimates with 95% confidence. Therefore, the 334 qualifying patients were recruited. Each patient was first listed on a preformulated excel spreadsheet, and relevant demographic and clinical data were then added using electronic medical records. The collected data included gender, age, serum creatinine, creatinine clearance, serum alanine transaminase (ALT), serum aspartate transaminase (AST), and daily platelet counts (for up to 14 days during linezolid treatment

Table 1 Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Patients aged 18 years or older • Admitted to an inpatient ward from January 2017 to December 2022 • Patients received intravenous linezolid for 48 hours or more • Baseline platelet count ≥ 150,000/mm^3 • Patient platelet count dropped by at least 50% or to <150,000/mm^3 within 14 days of starting linezolid therapy	• Patients younger than 18 years • Patients receiving intravenous linezolid for less than 48 hours • Baseline platelet count <150,000/mm^3 • Patient platelet count dropped by 50% or dropped to less than 150,000/mm^3 after 14 days of linezolid starting date • Patient received oral linezolid • Patient admitted before January 2017 or after December 2022

and up to 14 days after drug withdrawal). Days in which platelet counts were not measured were labeled as not applicable. Linezolid start and discontinuation dates were also recorded on the spreadsheet.

The data collection process adhered to the ethical standards of the Declaration of Helsinki. The institutional review board of DMC approved the study protocol before initiation of data collection (IRB number PH-23). Also, DMC IRB agreed for data collection without requirement for informed consent. This was because data were basically routine medical lab results collected directly from DMC electronic medical record system which is publicly opened without restriction for researchers who are DMC clinical staff as this study researchers. The list of patients included in the study was coded starting from 1 to 334 after data collection and before data analysis. Data saved to the personal computers of researchers under password protection to guarantee anonymity. Demographic data as well as the numbers and proportions of patients recovering from LIT on a given day were analyzed using Microsoft Excel. Results are reported as numbers, means, or percentages. StatPlus software was used for duration analysis, creating Kaplan–Meier curves, and calculating both mean and median times to LIT onset and time to recovery after linezolid stopped (TTRALS). Cumulative hazards are presented with 95% confidence intervals and statistical significance.

Results

Enrolled patients were predominantly middle-aged or older and most were male. Creatinine clearance was below normal in approximately half of all patients and less than 15 mL/min in 9%, indicating frequent mild renal dysfunction. However, fewer than 20% of the patients had baseline serum ALT and AST values higher than the upper normal range, so liver function was generally preserved. Baseline platelet count ranged from 150×10^9/L to 450×10^9/L in the vast majority of patients (85%). The mean duration of linezolid use was 10 days. Of the 334 patients enrolled, only 196 were included in the recovery analysis as platelet counts were not monitored during drug withdrawal in the others. Platelet count returned to normal in nearly half of all patients monitored for 14 days. Among this recovery subgroup, average recovery time was 5 days. Demographic and clinical variables are summarized in Table 2.

Table 2 Demographic Data of the Study Population

Parameter	Number	Percentage %	Parameter Mean	SD
Male	197	58.98		
Female	137	41.01		
Total	334			
Population age			60.7	17.98
Creatinine clearance			67.5	58.45
Serum creatinine more than 1.5	146	43.71	3.401	1.86
Creatinine clearance below 60 mL/min	190	56.88	30.631	14.70
Creatinine clearance below 30 mL/min	96	28.74	18.260	6.20
Creatinine clearance below 15	30	8.982	11.33	2.52
ALT more than 98 IU/L	35	10.47	208.85	147.40
AST more than 68 IU/L	63	18.86	217.29	319.83
Platelet baseline more than 450×10^9/L	50	14.97	603.25	146.70
Platelet baseline $150–450 \times 10^9$/L	284	85.92	256.19	82.43
Patients showing recovery of thrombocytopenia within 14 days after linezolid discontinuation	92	46.93		

Both mean and median time to LIT were around 5 days (5.43 and 5.0, respectively). At this time, the probability of LIT was 42% (Figure 1) and the cumulative hazard was 87% (Figure 2). Further, mean and median TTRALS were also around five days (5.2 and 5.0, respectively), with 42% probability of recovery failure and an 85% cumulative recovery rate (Figure 3). Within 6 days, the cumulative risk of thrombocytopenia was 100% and reached more than 200% by 10 days and 300% by 12 days. Cumulative recovery rate reached around 65% by day 4 and more than 100% by day 6 (Figure 4).

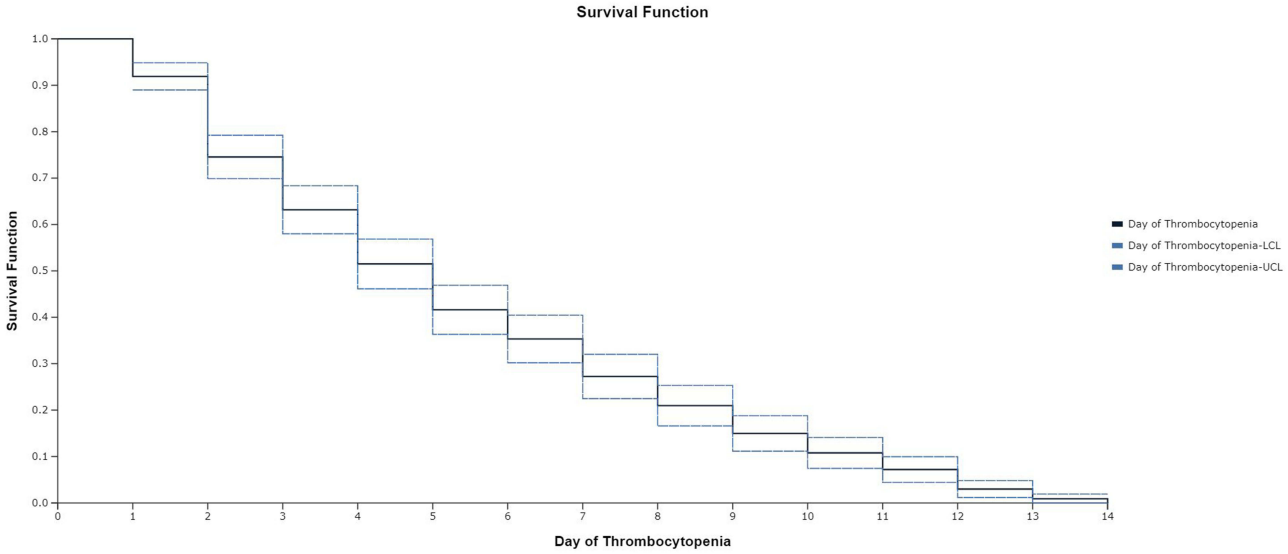

Figure 1 Time to linezolid-induced thrombocytopenia.

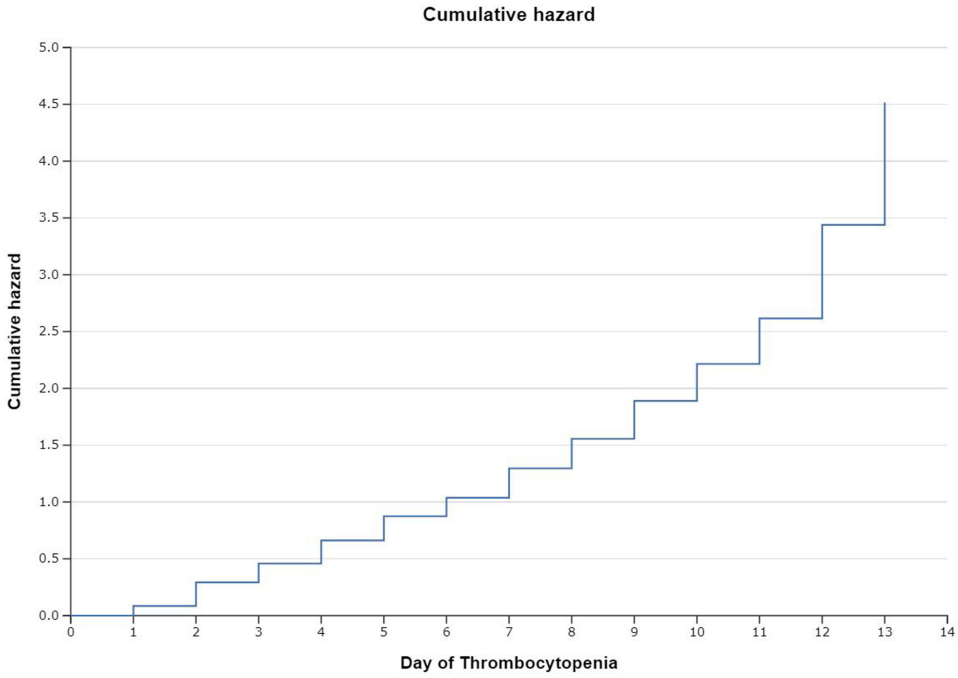

Figure 2 Cumulative hazard for linezolid-induced thrombocytopenia.

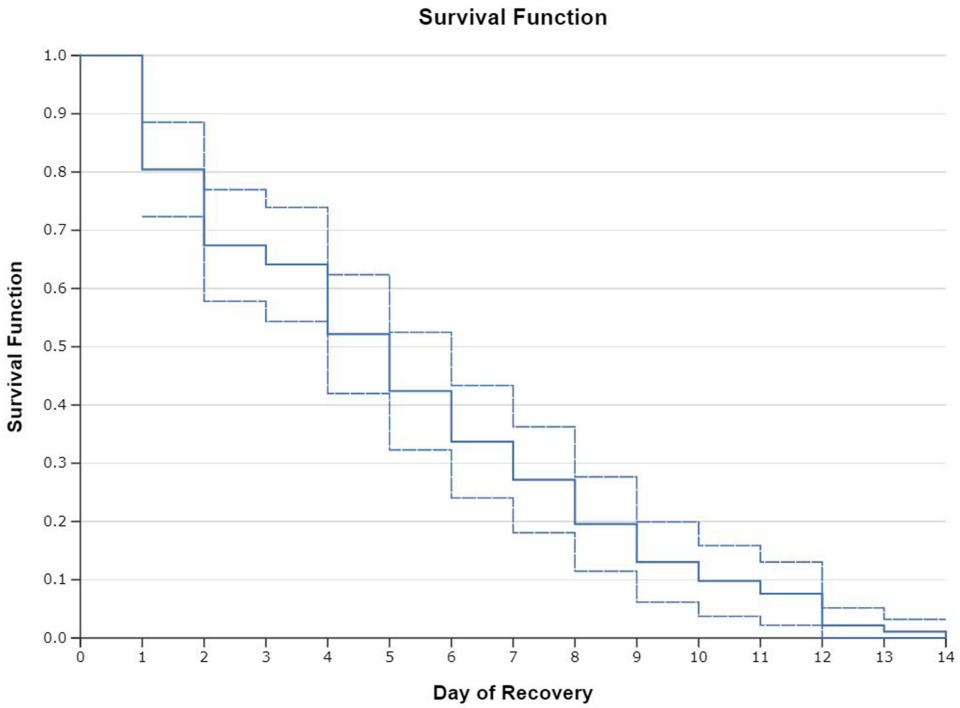

Figure 3 Time to recovery from linezolid-induced thrombocytopenia.

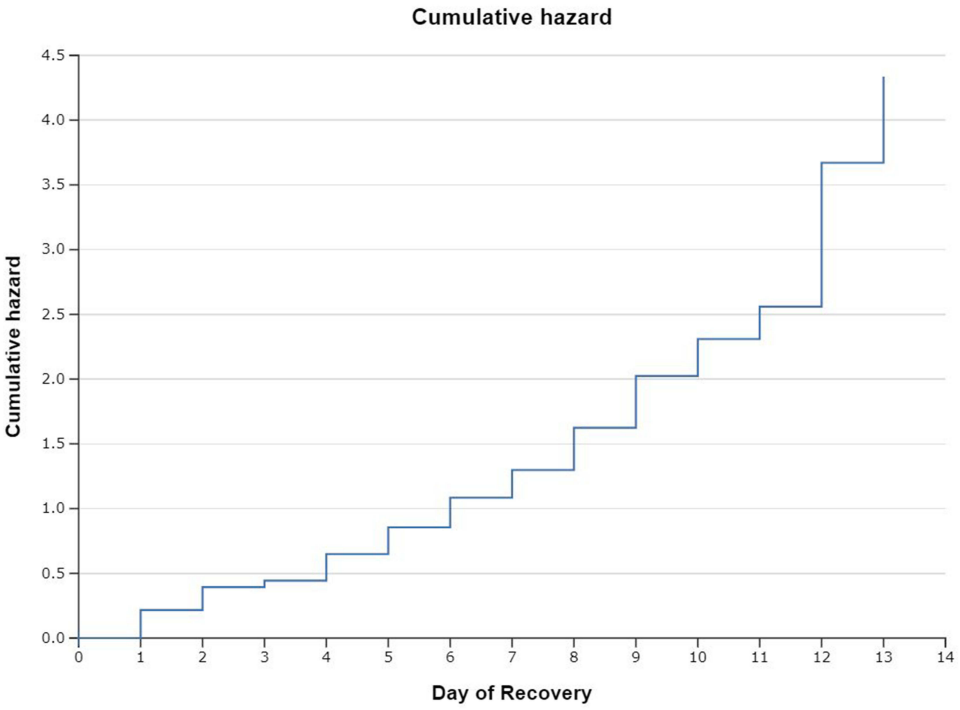

Figure 4 Cumulative hazard for recovery from linezolid-induced thrombocytopenia after discontinuation.

Discussion

Thrombocytopenia is a common and potentially life-threatening complication of linezolid therapy, but the treatment duration–risk relationship and recovery rate after linezolid withdrawal have varied across studies. This large-scale, single-center, retrospective study was designed to assess the daily probability of thrombocytopenia within 14 days of IV

linezolid initiation and to evaluate TTRALS using Kaplan–Meier survival analysis. In a large group of patients developing LIT within 14 days, both mean time to onset and recovery were relatively rapid compared to previous studies (about 5 days). For example, Hanai et al[9] reported that almost half of the study cohort developed LIT with median time of 9 days, Takahashi and colleagues reported a mean time to LIT onset of 7.4 ± 4.8 days,[6] and Giunio-Zorkin and Brown reported a mean time to LIT of 16 days (although the minimum was roughly equal to the mean and median reported in the present study).[3] In the current study, the cumulative hazard reached 87% by day five, implying that more than quarter of patients will develop thrombocytopenia by the fifth day of linezolid administration. Moreover, the cumulative hazard reach nearly 200% by day 9 and 400% by day 13, indicating that risk increased progressively with daily doses until at least day 14.

This study also successfully monitored the recovery of platelet count in 196 patients, a much larger sample than in previous studies.[3,6,8] Mean recovery time was 5 days, close to the 6 days reported by Giunio-Zorkin and Brown,[3] but substantially faster than the 12 days reported by Takahashi and colleagues.[6] Consistent with the current results, Cossu and coworkers reported a rise in platelet count over the first four days of linezolid withdrawal,[10] but again we found near complete recovery in about half of the patient population in this time frame.

Renal impairment is the most widely reported risk factor for LIT. Hanai and coworkers reported higher thrombocytopenia incidence among patients with severely impaired renal function (mean creatinine clearance rate of 21.5 ± 6.3 mL/min), including hemodialysis patients,[9] while Takahashi and colleagues concluded that time of LIT onset was shorter among patients with creatinine clearance lower than 50 mL/min.[6] In our cohort, mean creatinine clearance was 67.5 mL/min. Moreover, most patients were not on dialysis. Approximately half of the population did not possess renal impairment, indicating that the rapid rate of thrombocytopenia was caused by linezolid.

While linezolid is effective for infectious disease management, clinicians need to weigh the benefits against thrombocytopenia risk. However, the clinician should also consider the adverse effects and closely monitor the platelet count at baseline, during the entire treatment course and for 14 days thereafter, to confirm recovery and possibly prevent more serious complications, such as bleeding. The clinician should contemplate alternative antibiotic initiation with reduced risk of thrombocytopenia to avoid deteriorating the patient's condition. Future studies are needed to identify risk factors for LIT so that susceptible patients can be administered safer alternatives.

Indeed, a major limitation of this study is that we did not assess the impact of possible risk factors for LIT at baseline. This aspect should be addressed in future studies.

Conclusion

This large-scale, single-center, retrospective study indicates that LIT development and recovery can occur in around 5 days. Based on these findings, we suggest that all patients receive daily monitoring of platelet count during IV linezolid treatment and timely withdrawal in cases of thrombocytopenia.

Disclosure

The authors report no conflicts of interest in this work.

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