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ORIGINAL RESEARCH

Therapeutic Drug Monitoring of Linezolid in Drug-Resistant Tuberculosis Patients: Clinical Factors and Hematological Toxicities

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Purpose: Previous studies have indicated that the development of severe adverse events is associated with linezolid peak concentration (C_{max}), but the factors affecting linezolid C_{max} and evidences on therapeutic drug monitoring to anticipate toxicity in drug-resistant tuberculosis (DR-TB) patients have not been clarified clearly. This study aimed to explore the factors influencing linezolid C_{max} and investigate the association between linezolid concentration and hematological toxicity.

Patients and Methods: This study included patients with drug-resistant tuberculosis treated with linezolid from January 2022 to September 2023. We analyzed the factors affecting linezolid C_{max} using chi-squared and binary logistic regression. The diagnostic utility of linezolid C_{max} in predicting hematological toxicity was evaluated using receiver operating characteristic (ROC) analysis.

Results: A total of 76 patients were enrolled in the study. 63.20% met the standard rates for linezolid C_{max}. Age (P=0.036), weight (P=0.0016), and creatinine clearance (P=0.0223) significantly correlated with the C_{max}. Hematological toxicity was observed in 46.05% (35/76) of patients, characterized by thrombocytopenia (31.58%, 24/76), anemia (6.58%, 5/76), and leukopenia (21.05%, 16/76). ROC curve analysis confirmed the predictive value of linezolid C_{max} for thrombocytopenia with an area under curve of 0.728.

Conclusion: Suboptimal linezolid C_{max} was prevalent among patients with DR-TB, with age, weight, and renal function emerging as influential factors. Elevated linezolid C_{max} increases the risk of thrombocytopenia. Meticulous monitoring of linezolid C_{max} is imperative during anti-DR-TB therapy to tailor treatment and mitigate hematological toxicity.

Keywords: linezolid, therapeutic drug monitoring, influencing factors, hematological toxicity

Introduction

Tuberculosis (TB) is a significant contributor to morbidity and mortality on a global scale, serving as a primary etiological factor and prominent cause of death. Although the WHO Global Tuberculosis Report 2022 provides a cumulative reduction in the tuberculosis incidence rate from 2015 to 2021, the prevalence of drug-resistant TB (DR-TB) has escalated. There is a disparity between the identification and management of DR-TB, and the rate of successful treatment stands at a mere 60%.[1] Linezolid is the first oxazolidinone antibacterial agent that has strong anti-mycobacterial effects by binding to the 50S subunit of Mycobacterium tuberculosis ribosomes, inhibiting the connection of mRNA and ribosomes, and preventing the formation of the 70S initiation complex, thus blocking bacterial protein synthesis in the early stage of translation.[2] Linezolid is recommended as a first-line component of conventional regimens in patients with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) and those with additional resistance to fluoroquinolones (pre-XDR-TB), according to WHO guidelines.

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However, linezolid exhibits nonlinear pharmacokinetics with large interindividual variabilities.[3,4] Substandard plasma linezolid concentrations can lead to bacterial drug resistance, disease relapse, and treatment failure.[5] Findings from in vitro testing and molecular testing have indicated that 4.5–5.6% patients with MDR-TB in China exhibited linezolid resistance in 2022, which is the highest rate of linezolid resistance in the world.[6,7] Approximately 41% of patients were found to have inadequate serum levels of linezolid in the treatment of Gram-positive bacterial infections, and the factors that contribute to substandard blood levels include age, drug dose, enzymatic inducers, and hepatic dysfunction etc.[8] However, the clinical factors affecting plasma linezolid concentrations in DR-TB patients were not fully understood.

Linezolid-associated adverse drug reactions (ADRs) are prevalent among individuals with MDR-TB in programmatic settings, affecting up to 42% of patients.[9] Excessive linezolid exposure has been linked to an increased incidence of ADRs, particularly hematological toxicity. Monitoring the peak concentrations (C_{max}) of linezolid can help prevent the development of drug resistance and avoid potential toxicity. A meta-analysis of 23 studies reported a significant association between hematological toxicity and linezolid, with a combined proportion of 32.93% (95% CI: 23.13–45.54%, P<0.001).[10] Several studies have reported that linezolid concentration is associated with hematological toxicity, and heightened concentrations pose an increased risk of adverse hematological effects.[11–13] Previous studies have focused on the association between linezolid trough concentration (C_{min}) and ADRs. However, the conclusions differ greatly. Johannes Eimer et al reported C_{min} >2 mg/L are strongly associated with the development of severe mitochondrial toxicity in MDR-TB patients.[11] Chih-Ning Cheng et al reported the upper limit of C_{min} 9 μg/mL may improve platelet counts in Gram-positive pathogens patients.[14] Compared to C_{min}, monitoring linezolid C_{max} is more important for preventing the development of resistance and minimizing the risk of adverse effects. In this study, we discussed the clinical factors affecting linezolid C_{max} using a binary logistic regression model and assessed the association between linezolid C_{max} and hematological toxicity to optimize individual patient dosages, mitigate drug resistance, and enhance treatment efficacy for DR-TB.

Materials and Methods

Participants and Study Design

Patients with DR-TB admitted to the Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine between January 2022 and September 2023 were retrospectively studied. The inclusion criteria were as follows: age >18 years, linezolid treatment at 600 mg daily, regular use of linezolid to achieve steady-state plasma concentration (more than 5 half-time (3 days)). The exclusion criteria were poor compliance, immune system disease, use of immunosuppressants in the past three months, incomplete data.

This single-center retrospective cohort study was conducted in accordance with the Declaration of Helsinki (revised 2013). Patient informed consent was waived owing to the retrospective nature of the study, which was approved by the Medical Ethics Committee of Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine (No. [2021] trials (193)).

Data Collection

Demographic characteristics and clinical data were collected from each patient, including age, sex, weight, BMI, type of drug-resistant TB, duration of linezolid therapy, drug manufacturer, plasma peak concentration (C_{max}), hematological parameters, and biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), and serum albumin (ALB).

Definition of Steady-State Linezolid C_{max}

Linezolid steady state is reached following repeated administration more than 3 days (To monitoring hematological toxicity and linezolid C_{max} simultaneously, patients usually check their hematological parameters and linezolid C_{max} in the 7 days after linezolid treatment). For patients receiving a loading dose of linezolid, C_{max} was measured at 2 h after dosing under steady-state conditions. The samples were analyzed using high-performance liquid chromatography-mass spectrometry (HPLC-MS), according to the standard operating procedure for therapeutic drug monitoring. The guideline range of linezolid peak concentrations (C_{max}) in DR-TB patients (600 mg qd) is 12 ~ 26 mg/L.[15,16]

Outcome Definition

Hematological parameters were detected simultaneously on the day of TDM. Hematological toxicity was defined as follows: thrombocytopenia was defined as platelet count (PLT) <100 × 10^9/L or ≥30% reduction. Anemia was defined as hemoglobin (Hb) level <110 g/L or Hb≥30% reduction. Leukopenia was defined as white blood cells (WBC) <3.5*10^9/L or ≥30% baseline reduction. Baseline levels were defined as hematological parameters before linezolid therapy. Both criteria were required for patients with an abnormal baseline.[14,17,18] If patients were diagnosed with linezolid induced hematological toxicity, the patients will discontinue linezolid. If the patient's linezolid plasma concentration exceeds the therapeutic range but no ADR occurs, we will reduce the linezolid dose (300mg/d) to avoid ADRs.

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 and GraphPad Prism 10.0. Continuous variables conforming to a normal distribution are expressed as mean ± standard deviation (mean ± SD), whereas medians and interquartile ranges (IQR) are used to express non-normally distributed variables. Comparisons between two groups were performed using the independent samples *t*-test (normally distribution) and non-parametric Mann–Whitney U rank sum test (non-normally distribution), respectively. Categorical variables are expressed as percentages, and comparisons among groups were performed using the chi-square test or Fisher's exact probability test.

Results

Baseline Characteristics of the Patients

In this study, a cohort of 207 TB patients received linezolid treatment over 4 weeks. Patients were screened according to the inclusion and exclusion criteria, and 76 patients were included in the analysis (Figure 1). The median age of the included patients was 59 years, with an IQR of 39.5 to 69.25 years, comprising 53 males and 23 females. All the patients received linezolid 600 mg daily. A comprehensive summary of demographic and clinical characteristics is presented in Table 1. In the cohort, 35 patients (46.05%) developed hematological toxicity, including thrombocytopenia (31.58%, 24/76), anemia (6.58%, 5/76), and leukopenia (21.05%, 16/76). Notably, two patients who developed thrombocytopenia also developed anemia or leukopenia.

Linezolid Peak Concentration and Influencing Factors

The medium C_{max} of linezolid was 13.47 mg/L (10.41–15.34 mg/L). 63.20% (48/76) of the C_{max} conformed to the established therapeutic range (12–26 mg/L) and 5.24% (4/76) exceeded this range. Age (P=0.036), weight (P=0.0016), and creatinine clearance (Ccr) (P=0.0223) were significantly associated with the C_{max} of linezolid in the chi-square test (χ^2-test), whereas sex, AST, ALT, ALB, comorbidities, and manufacturer did not demonstrate significant associations (Table 2). These associations were further corroborated by the Mann–Whitney *U*-test (Figure 2). In addition, binary logistic regression was conducted using variables with significant differences. The analysis indicated that patients aged < 65 years had a 3.3-fold increased risk of lower C_{max} than those aged ≥ 65 years. Patients weighing > 60 kg had a 3.705-fold increased risk of a lower

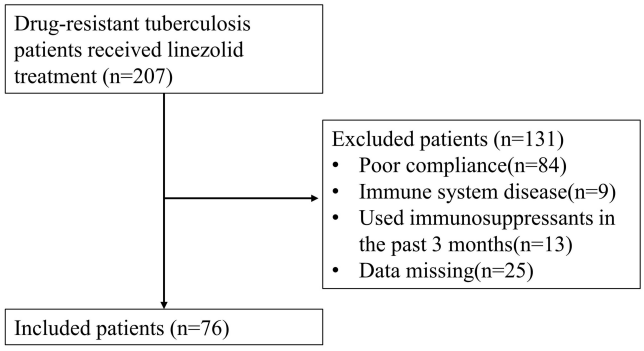

Figure 1 The patients' inclusion flow chart. 76 DR-TB patients were included in the analysis of linezolid concentration and hematological toxicity.

Table 1 Demographic and Clinical Characteristics of the Included Patients

Demographics	Total Patients (n=76)
Age (years)	59 (39.5, 69.25)
No. of male (%)	53 (69.73%)
Weight (kg)	57.78±11.64
Body-mass index (kg/m^2)	20.73 (17.96, 23.01)
Drug manufacturer (Pfizer/Hansoh)	34/42
Biochemical indicators	
Serum Albumin	36.3 (31.6, 40.1)
Creatinine clearance (Ccr, mL/min)	77.99 (55.5, 113.29)
Blood Urea Nitrogen (BUN)	4.865 (3.69, 6.28)
Alanine aminotransferase (ALT, U/L)	24 (14.75, 24.75)
Aspartate aminotransferase (AST, U/L)	20 (11.75, 34)
Comorbidities	
Diabetes mellitus	21 (27.63%)
Hypertension	15 (19.74%)
Chronic liver disease	12 (15.79%)
Lung disease	25 (32.89%)
Drug resistance level	
RR-TB/MDR-TB	43 (56.58%)
Pre-XDR-TB	25 (32.89%)
XDR-TB	8 (10.53%)
Linezolid treatment and concentration	
C_{max} (mg/L)	13.47 (10.41, 15.34)
Time of first TDM (days)	7 (5, 11)

Abbreviations: RR-TB, rifampicin-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis; Pre-XDR-TB, Pre-extensively drug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

Table 2 Univariate Analysis Results

Variable	Plasma Concentration (mg/L)		χ2	P
	<12	>12		
Gender				
Male	29 (78.38)	24 (61.54)	1.186	0.1778
Female	8 (21.62)	15 (38.46)		
Age (year)				
≧65	7 (18.92)	16 (41.03)	4.397	0.0360
<65	30 (81.08)	23 (58.97)		
Weight (kg)				
<60	13 (30.23)	30 (69.77)	9.976	0.0016
≧60	22 (66.67)	11 (33.33)		
Ccr (mL/sec)				
<80	16 (43.24)	27 (69.23)	5.219	0.0223
≧80	21 (56.76)	12 (30.77)		
AST (U/L)				
<40	28 (75.68)	31 (83.78)	0.3345	0.5630
≧40	9 (24.32)	6 (16.22)		
ALT (U/L)				
<50	31 (81.58)	33 (86.84)	0.09896	0.7531
≧50	7 (18.42)	5 (13.16)		

(*Continued*)

Table 2 (Continued).

Variable	Plasma Concentration (mg/L)		χ2	P
	<12	>12		
ALB (U/L)				
<35	11 (29.73)	20 (51.28)	2.814	0.0935
≧35	26 (70.27)	19 (48.72)		
Diabetes mellitus				
With	9 (24.32)	12 (30.77)	0.1379	0.7103
Without	28 (75.68)	27 (69.23)		
Hypertension				
With	6 (19.35)	9 (25.71)	0.1031	0.7482
Without	25 (80.65)	26 (74.29)		
Chronic liver disease				
With	2 (6.90)	10 (21.28)	1.812	0.1782
Without	27 (93.10)	37 (78.72)		
Lung disease				
With	10 (40.00)	15 (49.02)	0.2463	0.6197
Without	25 (60.00)	26 (50.98)		
Manufacturer				
Henjie	17 (45.95)	17 (43.59)	0.04262	0.8364
Zyvox	20 (54.05)	22 (56.41)		

Abbreviations: Ccr, Creatinine clearance; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALB, Albumin.

C_{max} than those weighing < 60 kg. Similarly, patients with normal renal function (Ccr >80 mL/sec) were more likely to experience a lower C_{max} than patients with renal impairment (Ccr <80 mL/sec) (Table 3).

Association Between Linezolid Concentrations and Hematological Toxicity

To investigate the association between linezolid concentration and hematological toxicity, we longitudinally assessed platelet counts, hemoglobin levels, and white blood cell counts before and after linezolid therapy. The results revealed a significant decrease in platelet count ($219*10^9$/L vs $179*10^9$/L, P=0.0002) following linezolid administration,

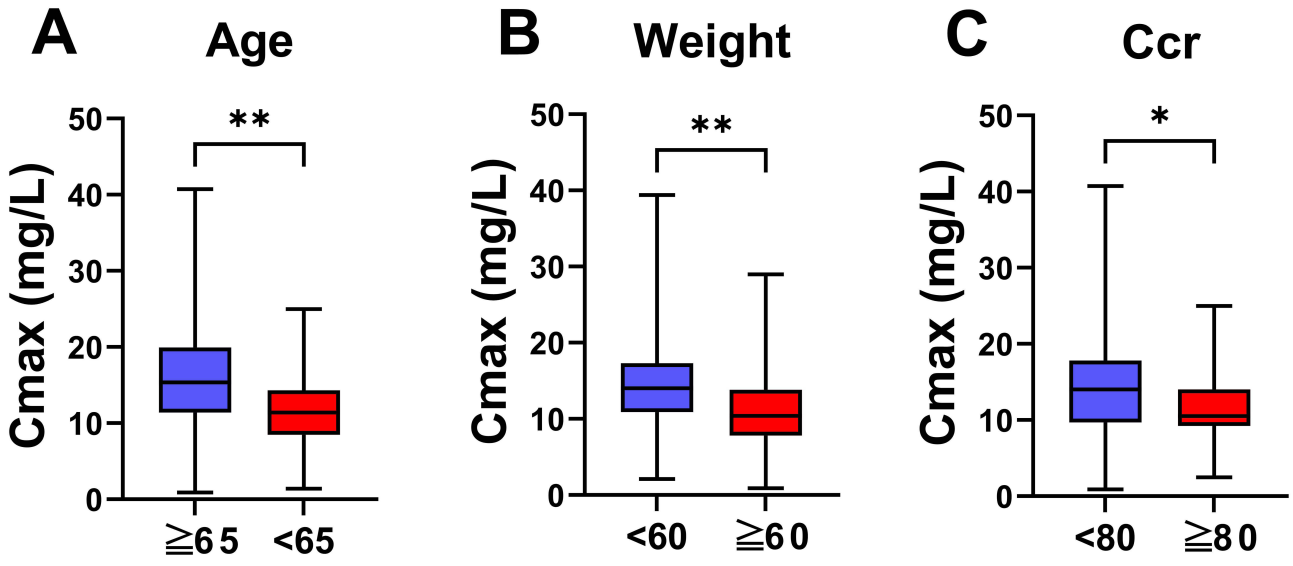

Figure 2 Univariate analysis results of linezolid. The Cmax between different age (**A**), weight (**B**), Ccr (Creatinine clearance) (**C**). *P< 0.05, **P<0.01.

Table 3 Multivariate Analysis Results

Variable	Coefficient	S $\bar{x}$	Wald χ^2	P value	OR (95% CI)
Age	1.219	0.580	4.412	0.036	3.383 (1.085, 10.551)
Weight	1.310	0.517	6.421	0.011	3.705 (1.345, 10.204)
Ccr	0.990	0.481	4.242	0.039	2.692 (1.049, 6.909)

whereas no notable alterations were observed in hemoglobin and white blood cell levels (Figure 3). Notably, patients manifesting thrombocytopenia demonstrated significantly higher linezolid plasma concentrations relative to those without this condition (14.24 mg/L vs 11.57 mg/L, P<0.05) (Figure 4). Furthermore, a receiver operating characteristic (ROC) curve was constructed to evaluate the prognostic potential of the linezolid plasma concentration for hematological toxicity. The results showed linezolid C_{max} > 13.58 mg/L were associated with an increased incidence of hematological toxicity, with an area under curve (AUC) of 0.728 (95% CI: 0.596–0.861, P=0.0143) (Figure 5).

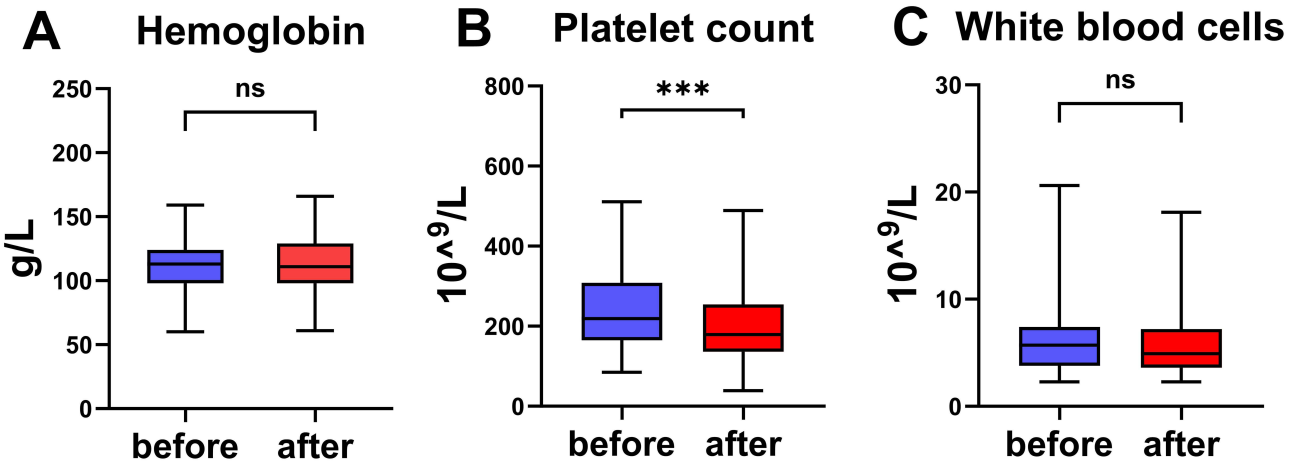

Figure 3 Biochemical indexes of patients before and after linezolid therapy. The change of hemoglobin (**A**), platelet count (**B**), white blood cells (**C**) before and after linezolid treatment. ***P<0.001, ns means no significance.

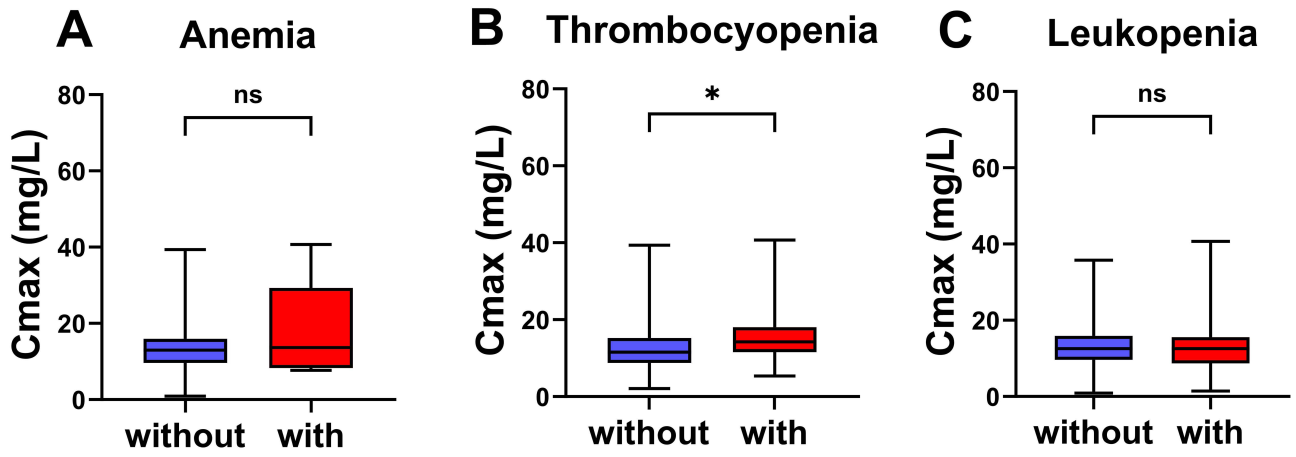

Figure 4 Distribution of linezolid concentrations in patients with or without hematological toxicity. Linezolid Cmax of linezolid with or without anemia (**A**), thrombocytopenia (**B**), leukopenia (**C**). *P<0.05, ns means no significance.

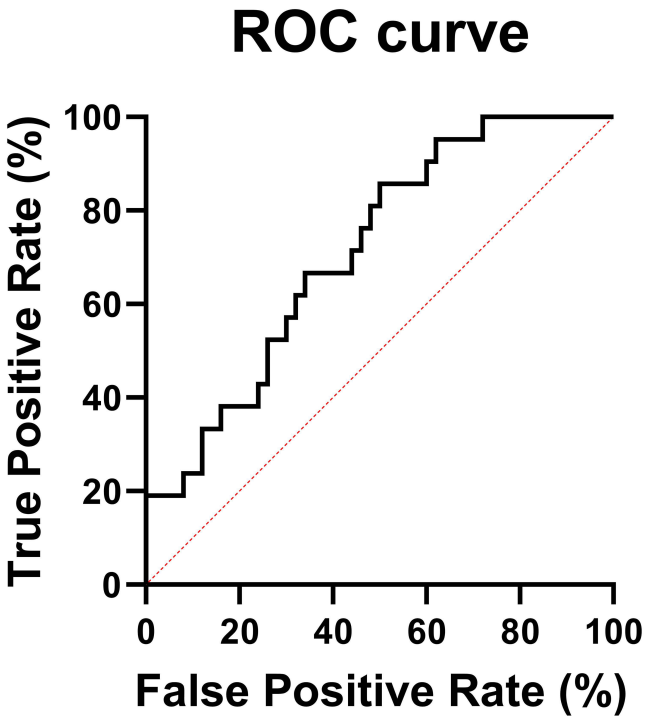

Figure 5 ROC curve for predicting hematological toxicity of linezolid C_{max}.

Discussion

Linezolid is rapidly and completely absorbed following oral administration. However, variability in the C_{max} of linezolid at 600 mg/day has been observed among patients.[19] Wang et al previously reported an average C_{max} of 15.6 ± 4.91 mg/L in a cohort of 65 TB patients with only 16.9% (11/65) displaying low concentrations.[20] Another study following oral dosing of 600 mg daily to a steady state observed a C_{max} of 16.2 (14.8–18.8) mg/L.[21] Padmapriyadarsini et al reported the median C_{max} was 18.3 mg/L at week 8 after treatment with linezolid 600 mg/d.[22] However, in our study, the median pharmacokinetic value (IQ range) of linezolid C_{max} was 13.47 (10.41, 15.34) mg/L, and only 63.20% of patients achieved standard plasma concentrations. Multiple logistic analysis demonstrated that age, weight, and creatinine clearance (Ccr) influenced linezolid plasma concentration.

Linezolid is partially excreted by the kidneys (approximately 35%), suggesting that renal dysfunction can lead to its accumulation, and consequently, elevated plasma concentrations.[23] A study conducted in Taiwan showed that patients with reduced creatinine clearance (<30 mL/min) had significantly higher plasma linezolid concentrations than those with a normal renal function.[14] This finding is congruent with that of a Japanese study that demonstrated a strong correlation between creatinine and linezolid clearance ($P<0.01$). Our study found the C_{max} of linezolid in patients with renal impairment (Ccr<80) was higher than patients with normal renal function (14.02 vs 10.51 mg/L). Individuals with a normal renal function are prone to experiencing inadequate drug exposure. Furthermore, those four patients whose C_{max} exceeded the therapeutic window (C_{max}>26 mg/L) presented with more severe renal impairment (Ccr<60). Therefore, it is important to monitor the C_{max} of linezolid regularly to avoid both insufficient and excessive exposure.

Patient weight also appeared to be inversely correlated with the linezolid plasma concentration. Our data revealed that the median C_{max} for patients weighing under 60 kg was notably higher than for those over 60 kg (14.00 vs 10.41 mg/L). This is consistent with the findings of previous studies, which reported that the C_{max} of linezolid in low-weight patients (59.3 ± 14.8 kg) was higher than that of large-weight patients (75.2 ± 18.2 kg).[24] Another study also elucidated low weight is a risk factor of elevated C_{min}.[25] When $C_{min} \geq 6.3$ mg/L, the probability of thrombocytopenia was more than 50%.[26] One plausible explanation for this observation is that the higher clearance rate in overweight people leads to an insufficient distribution of linezolid in the body, resulting in a lower plasma concentration.

Age was identified as a critical factor influencing linezolid C_{max} (OR=3.383, P=0.036). Under the same medication regimen, individuals over 65 years were more likely to achieve higher plasma concentrations compared to younger patients (15.34 vs 11.38 mg/L). This pattern was also seen in the subgroup of patients whose C_{max} surpassed the therapeutic range: all were older than 65 years, which aligns with previous literature. Under the regimen of 600 mg q12h, the trough linezolid concentration in patients over 70 years of age exceeded the guideline range of linezolid through multiple linear regression analysis.[27] The plasma linezolid level in elderly patients aged > 75 years was 2–3 times that in patients aged < 44 years.[28] Relevant studies have shown that elderly patients who are more prone to comorbid conditions, such as hepatic and renal impairments, might experience increased drug accumulation and, hence, higher plasma concentration.[29,30] Given the association between high plasma concentrations of linezolid and the risk of platelet reduction and other adverse drug reactions (ADRs), careful consideration of dosing in elderly patients with tuberculosis is imperative to minimize the risk of ADRs.

Hematological toxicity is the major cause of linezolid withdrawal. Numerous studies have been conducted on the risk factors for hematological toxicity of linezolid. However, the outcomes have been inconsistent.[31–33] It has been postulated that factors such as age, serum albumin levels, and creatinine clearance, which influence linezolid exposure, may be implicated in hematological toxicity. Our study aligns with existing evidence suggesting a link between linezolid C_{max} and hematological toxicity, particularly dose-dependent thrombocytopenia.[14] Linezolid-induced thrombocytopenia is believed to result from mitochondrial toxicity. Linezolid not only interacts with the ribosomes of Mycobacterium tuberculosis, but also with human mitochondrial ribosomes, leading to the inhibition of mitochondrial protein synthesis and subsequent thrombocytopenia.[34] Our study indicated minimal impact on hemoglobin and white blood cell levels following the administration of linezolid but a notable decrease in platelet count, which was consistent with previous results.[35–37] Furthermore, even within the therapeutic window, patients with thrombocytopenia had higher plasma concentrations of linezolid, underscoring its robust association with thrombocytopenia. ROC curve analysis demonstrated that linezolid C_{max} >13.58 mg/L could predict thrombocytopenia with 85.71% sensitivity and 52.94% specificity. If linezolid C_{max} was considered the only predictor of thrombocytopenia, 81.82% of patients were correctly identified. This prompted us to suggest a more credible hypothesize that an elevated linezolid C_{max} is associated with a high incidence of thrombocytopenia. However, it is important to note that the model overestimated the condition for 47.06% of the population. This was not a perfect positive correlation with thrombocytopenia, and linezolid C_{max} should be combined with clinical practice to reduce the risk of thrombocytopenia.

This study had several limitations. First, owing to its retrospective design, only patients with comprehensive datasets were included, which may have introduced a selection bias. Notably, because of the complex drug schedule and extended duration of tuberculosis treatment, patients often struggle to keep track of the different times, dosages, and frequencies of their drugs, 84 people with DR-TB were excluded due to poor compliance. Therefore, improving patient compliance is also an important part to improve the effectiveness of anti-tuberculosis treatment. Second, the relationship between the included variables and C_{max} was not adequately established and needs to be confirmed in a prospective randomized controlled study. Finally, the study utilized a singular 2-hour time point to assess plasma concentrations, which may not accurately represent the true peak levels across a diverse patient population, thus potentially masking individual pharmacokinetic variability.

Conclusion

In this study, suboptimal plasma concentrations of linezolid were frequently observed in patients with drug-resistant tuberculosis (DR-TB) in a clinical setting. The analysis identified age, weight, and creatinine clearance as independent predictors of linezolid C_{max}. A strong correlation was established between elevated linezolid C_{max} and the incidence of thrombocytopenia, and linezolid C_{max} >13.58 mg/L could partly predict the risk of developing this hematological complication. Therefore, the meticulous monitoring of linezolid C_{max} during anti-TB therapy is imperative. This practice facilitates the development of personalized treatment regimens and prevents hematological toxicity.

Ethics Approval and Informed Consent

This single-center retrospective cohort study was conducted in accordance with the Declaration of Helsinki (revised 2013) and approved by the Medical Ethics Committee of Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine (No. [2021] trials (193)). Waiving of informed consent was given due to the retrospective, non-interventional study design. All patient data were collected anonymously and ensured about the confidentiality of their information.

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Disclosure

The authors report no conflicts of interest in this work.

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