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Original Research Paper

Management of Linezolid-Induced Anemia in Drug-Resistant Tuberculosis Therapy: A Literature Review

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Abstract

Background: Linezolid is a Class A drug recommended for the treatment of multidrug-resistant tuberculosis (TB), but its use carries a significant risk of hematologic toxicity, particularly anemia. The optimal duration and dose for linezolid therapy are still not fully known. **Objective:** This systematic review aimed to evaluate strategies to manage anemia in patients with drug-resistant TB receiving linezolid therapy. **Methods:** Articles were searched through Science Direct, PubMed, and Google Scholar databases for articles published between 2014 and 2024. The keywords used were "tuberculosis resistant drugs", "linezolid", "hematology toxicity", and "anemia". **Results:** From the literature review, linezolid can cause anemia through the mechanism of inhibition of mitochondrial protein synthesis in erythropoiesis progenitor cells in the bone marrow and suppression of hematopoiesis. Major risk factors include long-term use (>8 weeks), high doses (>600 mg/day), and comorbid conditions such as malnutrition and liver disease. Management includes close monitoring of hemoglobin, dose reduction, discontinuation of therapy when necessary, and administration of hematopoietic supplements. **Conclusion:** Linezolid-induced anemia can significantly affect the continuation of therapy and quality of life of patients. The management strategies that can be applied depend on the severity of the anemia. Close monitoring and early intervention are essential to ensure successful treatment.

Keywords: linezolid; anemia; drug-resistant tuberculosis; hematologic side effects.

Introduction

Multi drug-resistant tuberculosis (MDR-TB) is a disease caused by *Mycobacterium tuberculosis* that have developed resistance to several first-line anti-tuberculosis drugs (OAT), thus requiring treatment with a second-line regimen. Currently, MDR-TB remains a major public health problem in many countries, including Indonesia. Based on the World Health Organization 2022 report, the incidence of MDR-TB reaches 500,000 cases per year worldwide, where only 30% of MDR-TB patients receive therapy[1]. Indonesia has 24,000 cases of MDR-TB, of which 2.4% of cases are new cases of MDR-TB, and 13% of cases are from MDR-TB with a history of re-treatment[2]. In 2019, 11,500 rifampicin-resistant TB (RR-TB) patients were diagnosed, with 48% starting second-line treatment and a 45% treatment success rate[3]. Indonesia has the second highest prevalence of TB in the world, and data from Central Sulawesi also shows that most TB patients are adults aged 19-25 years[4–6].

Since 2018, WHO has recommended Linezolid as one of the class A drugs in MDR-TB therapy. Linezolid is recommended always to be included in the therapy regimen unless there are contraindications[7,8]. Several clinical trials have proven the effectiveness of linezolid in improving the clinical outcomes of patients

with MDR-TB, and it is considered to be the most effective therapeutic regimen at present[9–11]. However, the use of linezolid carries a considerable risk of toxicity. In long-term use, such as in the treatment of MDR-TB or extensive drug resistance (XDR) TB, which often takes more than 6 months, linezolid is associated with serious side effects that are dose and duration-dependent, namely peripheral neuropathy, myelosuppression (anemia, thrombocytopenia, neutropenia), optic neuropathy, lactic acidosis, pancreatitis, and rhabdomyolysis[11–14].

This study is of high urgency given that linezolid-induced anemia is one of the significant hematologic side effects that can compromise the continuity of DR-TB therapy. The novelty of this study lies in its systematic approach to summarizing and analyzing the available scientific evidence on the management of linezolid-induced anemia in patients with MDR/XDR-TB, which has not been comprehensively reviewed. The impact of this study on clinical practice is to provide a stronger scientific foundation for clinicians in decision-making regarding early detection, monitoring, and therapeutic intervention of anemia, thereby improving patient adherence, reducing dropout rates, and optimizing outcomes of drug-resistant TB therapy.

Materials and Methods

Design Study

The use of a Systematic Literature Review (SLR) design is appropriate for synthesizing evidence on the relationship between linezolid use and anemia incidence among MDR-TB patients. The inclusion of a PRISMA flow diagram (Figure 1) enhances methodological transparency and replicability. However, it is recommended to clearly outline the PRISMA stages (identification, screening, eligibility, and inclusion) and provide the exact number of studies at each stage to ensure clarity in the selection process.

Sample

The inclusion criteria are well-defined, encompassing English-language original research articles (RCTs, cohort, cross-sectional, and case-control studies) focusing on adult DR-TB patients (≥18 years old) receiving regimens containing bedaquiline and linezolid within the publication range of 2014–2024. The exclusion of reviews, opinion papers, and short communications is well justified to maintain data validity and focus on primary research. Nevertheless, it would be beneficial to specify whether conference abstracts or unpublished studies were considered and how duplicate data were handled.

Data Collection

Data were collected through electronic literature searches using three main databases: PubMed, Cochrane, and ScienceDirect. The search was conducted independently by the researchers using the main keywords: “tuberculosis drug-resistant,” ‘linezolid,’ ‘anemia,’ and ‘hematology toxicity.’ These keyword combinations were formulated using Boolean operators (“AND,” “OR,” and “NOT”) to increase search precision. In addition, the Google Scholar database was also used as a supplement to ensure broader coverage of the literature. All retrieved articles were screened through a title and abstract screening process, followed by a full-text review to assess compliance with the inclusion and exclusion criteria. Data extracted from the selected articles included: (1) article identity (journal name, researcher name, and year of publication), (2) country where the study was conducted, (3) number of patient samples, (4) type of intervention provided, (5) research methodology design, and (6) outcomes.

Data Analysis

The use of descriptive and synthetic analysis is appropriate for summarizing findings and identifying patterns or associations between linezolid use and anemia incidence. The mention of quality assessment tools such as the Newcastle-Ottawa Scale (for observational studies) and PRISMA guidelines (for systematic reviews) supports methodological rigor. However, the section should be expanded to specify the procedure for quality appraisal, including whether two independent reviewers assessed study quality and how disagreements were resolved (e.g., through consensus or third-party adjudication). Additionally, a summary table of study quality scores could enhance interpretability.

Etical Consideration

The study appropriately emphasizes that it is based solely on secondary data from peer-reviewed scientific publications, with no direct involvement of human participants. The authors uphold research ethics principles, including integrity, methodological transparency, and respect for intellectual property rights. This ethical clarity aligns with international standards for secondary data research and supports the credibility of the review.

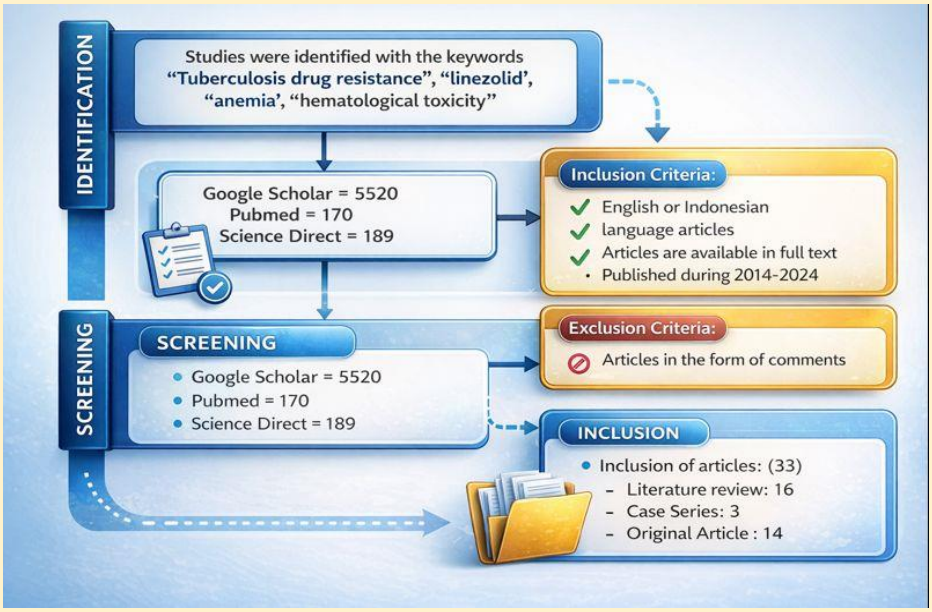

Figure 1. PRISMA Flow Diagram

Results

Drug Resistance Tuberculosis

Based on its type, TB drug resistance is classified into several categories. Monoresistance is when the bacteria are resistant to one type of first-line OAT, except rifampicin. Polyresistance occurs when there is resistance to more than one first-line OAT, but not the combination of isoniazid and rifampicin. MDR-TB is a form of resistance to isoniazid and rifampicin, with or without resistance to other first-line OATs. Pre-Extensively Drug Resistant (Pre-XDR) is MDR-TB accompanied by resistance to one of the fluoroquinolone class drugs or one of the second-line injectable drugs such as capreomycin, kanamycin, or amikacin. Meanwhile, Extensively Drug Resistant Tuberculosis (XDR-TB) is MDR-TB that is

also resistant to one fluoroquinolone and one second-line injectable drug. Finally, rifampicin-resistant tuberculosis (TB-RR) is a condition of resistance to rifampicin, which can stand alone as monoresistant or be part of poliresistant, MDR, or XDR.The mechanism of drug resistance in Mycobacterium tuberculosis is divided into two, namely intrinsic mechanisms and molecular mechanisms. Intrinsic mechanisms include a non-permeable cell wall, slow bacterial metabolism, and the presence of efflux pumps that remove drugs from the cell, thus reducing the effectiveness of treatment[15]. Meanwhile, molecular mechanisms are related to specific gene mutations that affect drug action. Rifampicin resistance is caused by mutations in the rpoB gene, especially in the "hot-spot" region, leading to changes in the structure of the RNA polymerase[16]. Isoniazid resistance generally occurs due to mutations in the katG and inhA genes, which inhibit drug activation and mycolic acid synthesis. Ethambutol becomes ineffective due to mutations in the embB gene, especially at position 306, which affects the synthesis of arabinogalactan in the cell wall. Meanwhile, resistance to pyrazinamide is caused by mutations in the pncA gene, which causes the loss of the pyrazinamide enzyme so that the drug cannot be converted to its active form[15,16].

Mechanism of Action of Linezolid in Drug-Resistant Tuberculosis Therapy

Linezolid is a first-generation oxazolidinone antibiotic that is effective against a wide range of gram-positive bacteria, including resistant strains such as MRSA and VRE. The drug has been approved for use since 2000 and is available in various dosage forms, namely intravenous, coated tablets, and oral suspension. Linezolid has an oral bioavailability of up to 100%, which allows easy transition between oral and intravenous preparations without any decrease in effectiveness. Peak plasma concentrations are reached within 0.5-2 hours after oral administration with plasma concentrations between 15-27 mg/L. The drug has a plasma protein binding of 31%, an elimination half-life between 3.4-7.4 hours, and a clearance rate of approximately 80 ± 29 mL/min. Linezolid is metabolized into two inactive metabolites, aminoethoxyacetic acid (metabolite A) and hydroxyethyl glycine (metabolite B). Since 2018, WHO has recommended linezolid as part of the core regimen (category A) for the treatment of patients with drug-resistant tuberculosis. The mechanism of linezolid against tuberculosis bacteria is through inhibition of protein synthesis by binding to the 30S and 50S subunits of the bacterial ribosome, which blocks the formation of the peptide initiation complex and inhibits the translation process[8,11,17]. Inhibition of these subunits causes inhibition of peptide chain complex formation and decreases the rate of protein translation. In some Gram-positive bacteria, linezolid can also reduce toxin production by inhibiting the expression of virulence elements[18].

Efficacy of Linezolid as a Therapy for Drug-Resistant Tuberculosis

Various studies have demonstrated linezolid's clinical efficacy in treating drug resistant-TB. A systematic review by Zhang et al. (2015) of 15 studies with 367 patients showed a therapeutic success rate of 83%[19]. Another meta-analysis by Agyeman and Ofori-Asenso (2016) of 507 patients reported a therapeutic success rate of 77.4% with a culture conversion rate of 88.4%[20]. Meanwhile, Lifan et al. (2019), in a meta-analysis of 72 studies, noted a sputum conversion rate of 93.2% and therapeutic success of linezolid was 67.4%[21]. Several randomized controlled trials (RCTs) have also shown results supporting the effectiveness of

linezolid. Lee et al. (2020) reported that TB-RO patients who received linezolid from the start of therapy experienced a culture conversion rate of 79%, compared to 35% in the group that received linezolid after two months[22]. The multicenter study by Tang et al. showed that therapeutic success was higher in the group receiving linezolid than in the control group (RR 2.36 vs. 0.26)[23]. A retrospective cohort study by Tack et al. (2021) of 117 XDR-TB patients with comorbid HIV treated with bedaquiline and linezolid combination recorded a therapeutic success rate of 75.2% with an average culture conversion on day 52[24]. In addition, a meta-analysis by Alene et al. (2022) found that the therapeutic success of MDR-TB in pregnant patients was higher in the group receiving linezolid (85%) compared to the group without linezolid (65.6%). However, the association with pregnancy outcome was not further discussed[25]. Two large clinical trials, Nix-TB and ZeNix, provided additional evidence for the effectiveness of linezolid in short-term regimens. The Nix-TB study evaluated a 6-month BPaL (bedaquiline-pretomanid-linezolid) regimen with a linezolid dose of 1200 mg/day and showed a culture seroconversion rate of 90%[17,26]. Meanwhile, the ZeNix study compared the effectiveness of BPaL with linezolid doses of 600 mg/day for 9 weeks and 26 weeks and found similar results (91% vs. 93%), with no significant differences[17]. These findings formed the basis of the WHO recommendation in 2022 that short-term therapy of DR-TB with BPaL regimens be given for 6 months. Currently, the standard dose of linezolid recommended by WHO and used in national TB control programs is 600 mg/day[12].

Epidemiology and Risk Factors of Linezolid-Induced Anemia

The Nix-TB clinical study (2020) showed that the administration of linezolid 1200 mg/day caused significant side effects such as peripheral neuropathy (81%), anemia (37%), and thrombocytopenia (6%), which often occurred in the first two months of therapy and led to discontinuation or dose adjustment[12,14,26]. Other studies in South Africa and by Graciaa et al. (2022) showed that long-term administration of linezolid 600 mg/day was safer, with most adverse events being mild and not requiring discontinuation[12]. The phase 3 ZeNix trial (2022) also supported that a dose reduction to 600 mg/day for 26 weeks reduced the incidence of neuropathy and myelosuppression[14]. Linezolid toxicity is influenced by clinical factors such as low Hb levels, renal impairment, comorbidities, and drug interactions. In addition, genetic differences such as mitochondrial polymorphisms and CYP450 2J2 enzyme expression also play a role[7,27–29]. Liu et al.'s meta-analysis (2022) recommended linezolid levels be kept ≤6-7 μg/mL to reduce hematologic side effects[30].

Mechanisms of Linezolid-induced-Anemia

Linezolid toxicity is influenced by clinical factors such as low Hb levels, renal impairment, comorbidities, and drug interactions. In addition, genetic differences such as mitochondrial polymorphisms and CYP450 2J2 enzyme expression also play a role[11]. As an anti-TB drug, Linezolid works by inhibiting bacterial protein synthesis through binding to the 50S and 30S ribosome subunits. However, because the structure of bacterial mitochondrial ribosomes is similar to that of humans, linezolid can also bind to human mitochondrial ribosomes, especially to the 23S rRNA unit. As a result, there is impaired expression of mitochondrial proteins and decreased activity of the enzyme cytochrome c oxidase, which plays a role in cellular respiration, thus inhibiting energy (ATP) production in hematopoietic precursor cells in

the spinal cord[7]. Due to mitochondrial toxicity, this leads to hematological side effects such as anemia and thrombocytopenia. Studies have also shown that linezolid increases the phosphorylation of myosin light chain 2, which inhibits platelet release from megakaryocytes, worsening the thrombocytopenia condition[31].

In addition to mitochondrial toxicity, linezolid-induced hematologic disorders may also be influenced by immune mechanisms and vitamin B6 deficiency, although the mechanisms are not fully understood[28,32]. Linezolid and its metabolites can form complexes with platelet membrane glycoproteins (GPIIb/IIIa) as well as IgG antibodies. These complexes are recognized by macrophages and destroyed by the reticuloendothelial system (RES), leading to thrombocytopenia. High amounts of IgG-linezolid-platelet complexes increase platelet destruction, exacerbating the cytopenic condition[11]. In addition, in vivo studies in animals show that linezolid can inhibit the process of erythropoiesis by suppressing the development of erythroblasts and other red blood cell precursors in the bone marrow, which contributes to the occurrence of anemia[11,33]. Anemia is also associated with elevated levels of Growth Differentiation Factor-15 (GDF-15), a TGF-β cytokine that increases under hypoxia, oxidative stress, and inflammation[11]. The increase in GDF-15 indicates a disturbance in erythropoiesis homeostasis due to long-term exposure to linezolid.

Linezolid-induced Anemia Therapy in Drug-Resistant Tuberculosis

Linezolid-induced hematologic toxicity can manifest in varying degrees of severity, ranging from mild to severe and potentially life-threatening. These manifestations include anemia, thrombocytopenia, leukopenia and even pancytopenia. In its management, clinicians need to consider the balance between the benefits and risks of continuing linezolid therapy. The EndTB Consortium provides management guidelines based on laboratory severity, which includes periodic monitoring, dose reduction to 300-600 mg/day, and temporary or permanent discontinuation in cases with severe toxicity[11]. In mild to moderate cases, dose reduction and close monitoring are effective. In severe cases, such as anemia with hemoglobin levels below 6.5 g/dL or platelets below 20,000/mm³, discontinuation of linezolid therapy should be immediate, and blood transfusion and erythropoietin administration may be considered.

Several studies have shown that administration of erythropoietin can increase hemoglobin levels in patients with linezolid-induced anemia, as shown in an in vivo study in rats and a case report of pure red cell aplasia[34]. However, the effectiveness of erythropoietin remains limited compared to discontinuation of therapy as a primary intervention[34,35]. Until now, there are no standardized guidelines regarding dose reduction schemes or reintroduction of linezolid therapy after toxicity. The Nix-TB study and pharmacokinetic model by Imperial et al. showed that a dose reduction from 1200 mg to 600 mg/day significantly reduced the incidence of peripheral neuropathy from 15% to 1% and the incidence of anemia from 17% to 2%. These model predictions also showed that a dose reduction could prevent severe anemia by 60%.[10,17]. In addition, Olayanju's study in XDR-TB patients showed that discontinuing or decreasing the dose of linezolid after three months of therapy did not affect the outcome of therapy, supporting a dose individualization approach[36].

Table 1. Management of Linezolid-induced Hematologic Toxicity [11].

Degree 1	
Criteria	**Management**
Hb 9.5-10.5gr/dl Plt 75.000-99.999(/mm^3) Leu 3000-LLN (/mm^3) ANC 1000-1500 (/mm^3)	- Periodic monitoring - Decrease the dose of linezolid to 300mg/day or 600mg for 3x in one week
Degree 2	
Hb 8.0-9.4gr/dl Plt 50.000-74.999 (/mm^3) Leu 2000 – 2999 (/mm^3) ANC 750-999 (/mm^3)	- Monitoring. - Decrease the dose of linezolid to 300mg/day or 600mg for 3x in one week - If there is grade 2 neutropenia, immediately stop linezolid administration - Consider erythropoietin administration - Linezolid administration can be reconsidered if the degree of toxicity improves to grade 1
Degree 3	
Hb 6.5-7.9gr/dl Plt 20.000-49.000 (/mm^3) Leu 1000-1999 (/mm^3) ANC 500-749 (/mm^3)	- Discontinue linezolid therapy immediately - If there is grade 3 anemia, consider giving erythropoietin - Linezolid administration can be reconsidered if the degree of toxicity improves to grade 1
Degree 4	
Hb < 6.5gr/dl Plt < 20.000 (/mm^3) Leu < 1000 (/mm^3) ANC < 500 (/mm^3)	- Discontinue linezolid therapy immediately - Consider blood transfusion or erythropoietin administration - Linezolid administration can be reconsidered if the degree of toxicity improves to grade 1

In patients with chronic kidney disease, a study by Kawasuji showed that giving a lower dose of linezolid at the beginning of therapy decreased the risk of thrombocytopenia compared to giving the standard dose. However, the association with anemia has not been further studied.[37]. As the risk of toxicity increases with the duration of therapy, close hematologic monitoring is very important. Several studies have reported that pancytopenia generally appears after more than 20 days of therapy, and symptoms improve after 2-3 weeks of discontinuation[10,29,38]. The WHO and other institutions, such as the United States Agency for International Development TB CARE and the Curry International TB Center, recommend complete blood tests before starting therapy, then weekly in the first month and continuing monthly or based on symptoms[11]. In addition, therapeutic monitoring of drug levels is also recommended, maintaining an AUC/MIC ratio of ≥100 as an efficacy target[11]. The study of Bolhuis et al. showed that a dose reduction to 300 mg/day or even 150-200 mg/day can still be maintained as long as the AUC/MIC ratio is high without reducing the effectiveness of therapy[39]. The Imperial study also noted that a decrease in hemoglobin levels of more than 10% from baseline in the first 4 weeks of therapy had high sensitivity and specificity in predicting the incidence of severe anemia[17]. Therefore, a close monitoring approach, accompanied by clinical and pharmacokinetic-based dose adjustments, is essential to minimize linezolid's hematological toxicity without compromising tuberculosis therapy's efficacy.

Conclusion

Linezolid is effective as a recommended regimen A for MDR-TB therapy but has side effects of myelosuppression, especially anemia. This effect is caused by mitochondrial toxicity in the bone marrow and immunological mechanisms that trigger the destruction of erythrocytes and platelets, which mainly appear when taken for more than 28 days at doses greater than 600mg/day. The management of Linezolid-induced anemia depends on the severity, ranging from monitoring and dose reduction to drug discontinuation. Monitoring blood and reticulocytes is important every week in the first month, then once a month. Research on the optimal dose of Linezolid is still ongoing.

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