Multidrug-resistant tuberculosis (MDR-TB) is caused by an organism that is resistant to both rifampicin and isoniazid. Extensively drug-resistant TB, a rare type of MDR-TB, is caused by an organism that is resistant to quinolone and one of group A TB drugs (i.e., linezolid and bedaquiline). In 2018, the World Health Organization revised the groupings of TB medicines and reclassified linezolid as a group A drug for the treatment of MDR-TB. Linezolid is a synthetic antimicrobial agent in the oxazolidinone class. Although linezolid has a good efficacy, it can cause substantial adverse events, especially hematologic toxicity. In both TB infection and linezolid mechanism of action, mitochondrial dysfunction plays an important role. In this concise review, characteristics of linezolid as an anti-TB drug are summarized, including its efficacy, pathogenesis of hematologic toxicity highlighting mitochondrial dysfunction, and the monitoring and management of hematologic toxicity.

**Keywords:** MDR-TB; XDR-TB; Linezolid; Hematologic Toxicity; Mitochondria
announced updated guidelines on the treatment of drug-resistant TB. Most MDR/XDR-TB patients can be treated with solely oral drug regimens without the use of injectable drugs\(^6\). Through collaboration, the American Thoracic Society, Centers for Disease Control and Prevention, the European Respiratory Society, and the Infectious Diseases Society of America released guidelines for the treatment of drug-resistant TB in November 2019. These guidelines have prioritized the use of an all-oral regimen. Linezolid is recommended in the regimen for MDR-TB\(^6\). However, the use of linezolid has a substantial risk of toxicity. Its optimal dose and duration remain undefined. On the other hand, linezolid is safe and well tolerated when it is used in short courses (<28 days) for infections other than TB\(^7\). In cases with a longer treatment, such as when its used for MDR/XDR-TB treatment (typically 6 months or longer), linezolid is associated with frequent serious, dose-dependent, and duration-dependent adverse effects, including anemia, neutropenia, thrombocytopenia, peripheral neuropathy, and more rarely, optic neuropathy, thrombocytopenia, and rhabdomyolysis\(^7\). A detrimental event (particularly hematological, neurological, and gastrointestinal) was experienced in 58.9% subjects, mostly in a cohort of individuals treated with an oral daily dosage >600 mg\(^8,9\). These adverse events can result in early cessation or reduction in the dose, which may compromise the efficacy of the drug.

Risks and predictor factors for hematological toxicities with linezolid remain unclear. The current focus is primarily on the efficacy and toxicity of a linezolid regimen in MDR-TB and XDR-TB. Comprehensive review of linezolid itself is limited, including pathogenesis, risk factors of hematologic toxicities, and on how to monitor and manage any problems that might occur. Linezolid inhibits mitochondrial ribosomes, which might be the cause of hematological alterations. However, little is known about the mechanisms involved in linezolid-associated mitochondrial toxicity in humans\(^10,11\).

Because of the importance of linezolid in the treatment of MDR/XDR-TB and the high number of reports on its hematologic toxicities, the goal of this review is to increase awareness and understanding of hematologic toxicities of linezolid in MDR/XDR-TB with a focus on the role of mitochondria.

**Data Sources**

The databases searched were Medline via PubMed, Cochrane Database of Systematic Reviews via Ovid, and Embase (January 2000 to July 2020). Searches were performed in July 2020. Data for this review were identified by searches of PubMed using “multidrug resistant tuberculosis,” “extensively resistant tuberculosis,” and “linezolid” as free text and MeSH terms in combination with other terms including “hematologic toxicity,” “bone marrow suppression,” or myelotoxicity (Figure 1).

**Linezolid: Drug invention, Chemistry, Mode of Action, and Pharmacology**

1. **Drug invention**

Linezolid was discovered in the mid-1990s. It was approved for commercial use in 2000 as an antibiotic for the treatment of all major Gram-positive bacterial pathogens of humans\(^12\). Linezolid is a synthetic antimicrobial agent in the oxazolidinone class. Since its approval in 2000, it has remained the primary drug in that class. It is used in therapy because of its distinctive mode of action, which involves inhibition of protein synthesis. As a synthetic antibiotic, linezolid can block the biosynthesis of bacterial proteins by binding to rRNA on both the 30S and 50S ribosomal subunits\(^13\).
2. Chemistry

The empirical formula of linezolid is C_{16}H_{20}FN_{3}O_{4} (molecular weight: 337.35 g/mol) (Figure 2). Studies on structure–activity relations of oxazolidinones have indicated that the N-aryl group and 5-S configuration are crucial for its activity. The 5-acylaminomethyl group is all important for its activity. Its activity is high because of the electron-withdrawing group in the aryl ring. Extra-replacement on the proximal aromatic ring does not affect its antibacterial activity, although it can change its solubility and pharmacokinetics.

3. Pharmacokinetics

Oral absorbance of linezolid is remarkable, with 100% bioavailability. It is not influenced by food. An intravenous route can be changed to an oral one in clinically stable patients. The plasma protein-binding level of this molecule is approximately 31%. The plasma half-life of linezolid is 3.4 hours to 7.4 hours. Linezolid has volume distribution that approximates whole-body water content of 40–50 L. The compound is metabolized to inactive metabolites, including hydroxyethyl glycine and aminoethoxy-acetic acid. Linezolid has a clearance rate of 80±29 mL/min through both nonrenal and renal mechanisms. Renal tubular reabsorption may occur. An unaltered form of some fraction of its dose is excreted in urine.

After a five-fold increase in dose, a low level of nonlinearity was found, with a 30% decrease in clearance. Elderly patients, those with mild to moderate hepatic damage or mild to moderate chronic renal failure, and healthy or young volunteers show no difference in plasma concentration. A seven- to eight-fold increase in exposure to drug metabolites has been reported in patients with severe renal impairment on dialysis than in patients with normal renal function. Clearance of linezolid is higher in children than in adults. Therefore, higher daily doses of drug per kilogram of body weight are required in children than in adults.

4. Pharmacodynamics

Linezolid is an antimicrobial agent with a long duration and time-dependent activity. The value of the area under the curve/minimum inhibitory concentration (AUC/MIC) and the time that the plasma concentration is above the MIC (MIC) are used as parameters to evaluate pharmacodynamics. Linezolid has a post antibiotic effect. The best pharmacokinetic/pharmacodynamics parameters to determine its activity are time with serum concentrations higher than the minimum inhibitory concentration (T > MIC) and the AUC/MIC ratio. Linezolid is primarily a bacteriostatic antimicrobial agent. T > MIC of at least 40% is predictive of its efficacy. In healthy volunteers, this objective can be achieved for pathogens with MICs of 2–4 mg/L by administering 600 mg intravenously twice a day.

Efficacy of Linezolid Regimen for MDR-TB and XDR-TB

Most trials of linezolid effects on TB included subjects with MDR-TB and XDR-TB. Efficacy of linezolid in treatment of drug-resistant TB has been evaluated in several reviews. Zhang et al. have conducted a systematic review and meta-analysis of 15 studies (367 patients). They found that 83% (95% confidence interval [CI], 75%–90%) of outcomes were favorable (either cure or treatment completion). The pooled rate of culture conversion was 89% (95% CI, 83%–95%). Of those 367 patients, 46.3% had XDR-TB. Cox and Ford have reviewed 11 studies (148 patients). They found that the pooled proportion for treatment success was 67.9% (95% CI, 58.0%–78.9%). Of those subjects, 28% had XDR-TB. Agyeman and Ofori-Asenso have conducted systematic review and meta-analysis of 23 studies in 14 countries involving 507 patients. The pooled proportion for treatment success was 77.4% (95% CI, 71.4%–82.8%), with a culture conversion rate of 88.4% (95% CI, 83.8%–92.4%). Lifan et al. have conducted systematic review and meta-analysis of 72 original studies that included 302 patients with XDR-TB treated with linezolid. Pooled estimates for sputum culture conversion and treatment success rates were 93.2% and 67.4%, respectively.

Individual patient analysis has been reported in three meta-analyses. Sotgiu et al. have reported individual data from 121 patients treated with linezolid. Pooled estimates of anti-TB treatment success and culture conversion were 82% and 93%, respectively. Median time to sputum smear and culture conversion were 43.5 days and 61 days, respectively. Chang et al. have evaluated 194 patients from 20 articles. They found that linezolid increased the probability of favorable outcome by 55% (10% to 121%). Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment-2017 have evaluated 12,030 patients from 25 countries in 50 studies. The overall treatment success rate was 61% (n=7,346). However, 1,017 patients (8%) suffered failure or relapse and 1,729 patients (14%) died. Treatment success was positively associ-
ated with the use of linezolid (adjusted risk difference, 0.15; 95% CI, 0.11–0.18) compared with failure or relapse.

Two randomized studies have found improved treatment outcomes with linezolid in XDR-TB. Lee et al.22 have evaluated 41 patients with XDR-TB. They found higher culture conversion at four months after randomization (relative risk [RR], 2.26; 95% CI, 1.19–4.28) when linezolid was given immediately than with a delay of two months. By four months, 15 of 19 patients (79%) in the immediate-start group and seven of 20 (35%) in the delayed-start group had culture conversion (p=0.001).

Tang et al.21 have conducted a multicenter, prospective, randomized, controlled study of 65 subjects with XDR-TB. They found a significantly higher cure rate (RR, 2.36; 95% CI, 1.13–4.90) and a lower failure rate (RR, 0.26; 95% CI, 0.10–0.70) in subjects treated with linezolid than in those who were not. The proportion of sputum culture conversion in the linezolid therapy group was 78.8% by 24 months, significantly higher than that in the control group (37.6%, p<0.001). The treatment success rate in the linezolid therapy group was 69.7%, significantly higher than that in the control group (34.4%, p=0.004).

Mitochondria in TB and Linezolid Toxicity

1. Mitochondria in TB

Mitochondria have important roles in the cell death pathway and TB infection.24-26 Mycobacterium tuberculosis (Mtb) targets mitochondria to increase replication by disturbing the cellular death pathway in alveolar macrophages.27 Mtb secretes proteins that can cause changes in their structures (size, form, number, distribution, fragmentation) and functions of mitochondria. Inhibition of mitochondrial function can lead to increased growth of Mtb and persistent infection.28-30

Necrosis and apoptosis are the two processes that can affect macrophages in TB infection. Infection with a virulent strain (H37Rv) of Mtb can cause damage to mitochondrial membranes in macrophages, increasing cytochrome c release from intermembrane spaces and causing further necrosis.20,30 Necrosis of macrophages caused by Mtb is the mechanism involved in the further dissemination of the pathogen and disease development.28

Infection with an attenuated Mtb strain (H37Ra) can cause apoptosis of macrophages, which can retain Mtb in apoptotic bodies to inhibit pathogen dissemination. Apoptosis of macrophages promotes antibacterial activity by increasing antigen presentation, allowing the innate immune system to reduce infection.26

2. Mitochondria in linezolid toxicity

Linezolid inhibits bacterial protein synthesis and further interferes with the growth of bacteria by a mechanism that involves disturbance of bacterial mitochondrial22,31. Mitochondria are important organelles that can initiate or amplify signals of apoptotic cell death.32,33. Mitochondria originated as ancient proteobacteria engulfed by eukaryotic cells in order to obtain energy from utilization of oxygen. Therefore, there are evolutionary resemblances between mitochondrial and bacterial ribosomes. Interactions between ribosomal-inhibitor antibiotics such as linezolid and the host can have severe clinical effects common to primary mitochondriopathies.30-32,35

Linezolid can bind to mitochondrial ribosomes, damage the expression and biosynthesis of mitochondrial proteins encoded by the mitochondrial genome, and block the action of cytochrome c-oxidase and mitochondrial oxidative activity.31,34. The degree of exposure of a microorganism to this antibiotic as estimated by the AUC/MIC ratio is associated with the effectiveness of linezolid. Inhibition of mitochondrial ribosomes is also correlated with the level of linezolid exposure.36. However, little is known about linezolid tissue specificity. Mitochondrial haplogroup U, mutations in 12S rRNA, and m.2706A>G, m.3197T>C, and m.3010G>C A polymorphisms in 16S rRNA tend to be associated with increased mitochondrial and clinical adverse effects.37

Hematologic Toxicity

1. Pathogenesis of hematologic toxicity

Suppression of bone marrow by linezolid is usually related to dose and duration of treatment, although it occurs infrequently during days 10–14 after drug administration.38. Two possible mechanisms are considered to be responsible for thrombocytopenia side effects. One is bone marrow suppression of platelet production11-43. Linezolid can increase myosin light chain 2 phosphorylation, followed by repression of platelet release from mature megakaryocytes in an in vitro investigation using human megakaryoblast (MEG-01).32. The second mechanism is increased platelet destruction due to an immune mechanism.32-44

Linezolid and its metabolites can bind to glycoprotein membrane IIb/IIIa to form IgG antibody complex by fragment antigen-binding. The fragment crystallizable portion can attach to macrophages. The reticuloendothelial system then destroys the platelet–linezolid–IgG complex.34

An in vitro study with mice has shown that linezolid can affect precursor colony forming unit–erythroblasts, burst forming unit–erythroblasts, and erythroblasts in bone marrow.45. Linezolid can repress the proliferation and cellular metabolite activity and interfere with mitochondrial function.
Linezolid can also block mitochondrial protein biosynthesis and decrease ATP production in bone marrow precursor cells. Mechanisms underlying linezolid-induced anemia are currently unclear. However, vacuolated pronormoblasts suggest the mechanism of anemia is identical to that of chloramphenicol-induced myelosuppression. Suppression of mitochondrial respiration via inhibition of mitochondrial protein synthesis is likely the mechanism. Pure red cell aplasia has also been reported as one mechanism of linezolid-induced anemia.25,46

Figure 3 shows a schematic of linezolid-induced hematologic toxicities.

2. Incidence

The incidence of myelosuppression (anemia or neutropenia), anemia, and thrombocytopenia associated with the use of linezolid is shown in Table 1.

Table 1. Incidence of hematologic toxicity of linezolid

| Reference         | Incidence of hematologic toxicity (%) | No. (subjects) | Starting dose (mg/day) |
|-------------------|--------------------------------------|----------------|------------------------|
| Attassi et al.44  | NA NA 32 19 1,200                    | 19             | 1,200                  |
| Birmingham et al.47 | NA 4.1 7.4 796 | 796           | 1,200                  |
| Niwa et al.48     | NA NA 17 42 1,200                    | 42             | 1,200                  |
| Takahashi et al.49 | NA NA 32.8 331 | 331           | 1,200                  |
| Sotgiu et al.8    | NA 38.10 11.8 121 450–1,200         | 121            | 450–1,200              |
| Koh et al.36      | 4 NA NA 51 300                      | 51             | 300                    |
| Tse-Chang et al.31 | 85 NA NA 13 600      | 13             | 600                    |
| Agyeman et al.18  | 32.9 (95% CI, 23.1–43.5) NA NA 507 | 507            | 300–1,200              |
| Conradie et al.32 | 48 NA NA 109 1,200                  | 109            | 1,200                  |

NA: not available.
Risk Factors for Hematologic Toxicity of Linezolid

Risk factors for hematologic toxicity are shown in Table 2. Figure 4 provides a schematic summary of the role of mitochondria in TB and hematologic toxicity of linezolid.

Monitoring

When using linezolid, it is necessary to monitor blood counts (weekly during initial phase, then monthly) and signs and symptoms of peripheral neuropathy and retinitis. Monitoring varies considerably among studies. Natsumoto et al. measured platelet counts two to three times per week. Hanai et al. assessed hematological and biochemical parameters after four days of linezolid treatment. Conradie et al. evaluated side effects of treatment weekly to week 16, at weeks 20 and 26, and then at one, two, and three months after the end of treatment and every three months thereafter to 24 months after the end of treatment.

In 2016, the Curry International Tuberculosis Center recommended complete blood counts monthly for patients on linezolid. The United States Agency for International Development Tuberculosis CARE recommends a complete blood count check before starting linezolid, weekly during the first month, and then monthly, with additional checks if there are any symptoms or signs of myelosuppression.

The World Health Organization recommends monitoring for linezolid treatment, with hemoglobin and white blood cell count monitored weekly at first and then monthly or as needed based on symptoms. Any adverse events throughout

Table 2. Risk factors for hematologic toxicity of linezolid

| Risk factor                                      | Study design                                      | Reference                                      |
|-------------------------------------------------|--------------------------------------------------|------------------------------------------------|
| Hemoglobin pre-treatment <10.5 g/dL             | Case control                                     | Senneville et al.                              |
| Platelet count                                  | Case report and literature review                 | Luo et al.                                     |
| Baseline platelet count <173,000/mm³             | Clinical trial                                   | Gerson et al.                                  |
| Baseline platelet count <240,700/mm³             | Prospective observational                        | Grau et al.                                    |
| Baseline platelet count <90,000/mm³              | Observational retrospective cohort                | Gonzalez-Del Castillo et al.                  |
| Baseline platelet level of <200,000/mm³          | Retrospective                                    | Kaya Kilic et al.                              |
| Dose                                            |                                                   |                                                |
| Daily dosage >18.7 mg/kg/day                     | Retrospective                                    | Chen et al.                                    |
| Doses >600 mg/day                               | Systematic review and meta-analysis              | Agyeman and Ofori-Asenso                       |
| Duration                                        |                                                   |                                                |
| >14 days                                        | Clinical trial                                   | Gerson et al.                                  |
| >10 days                                        | Open-label, noncomparative, nonrandomized clinical trial | Birmingham et al.                            |
| Renal function                                  |                                                   |                                                |
| Creatinine clearance <88.3 mL/min/1.73 m²       | Retrospective                                    | Chen et al.                                    |
| Creatinine clearance rates of <60 mL/min        | Retrospective                                    | Hanai et al.                                   |
| Hemodialysis                                    | Retrospective                                    | Hanai et al.                                   |
| Renal failure: creatinine clearance <50 mL/min  | Observational retrospective cohort                | Gonzalez-Del Castillo et al.                  |
| Serum albumin concentration <33.5 g/L           | Retrospective                                    | Chen et al.                                    |
| Cerebrovascular disease                         | Observational retrospective cohort                | Gonzalez-Del Castillo et al.                  |
| Moderate or severe liver disease                | Observational retrospective cohort                | Gonzalez-Del Castillo et al.                  |
| Malignancy                                       | Observational retrospective cohort                | Gonzalez-Del Castillo et al.                  |
| Combination therapy                             |                                                   |                                                |
| Caspofungin and levofloxacin therapy            | Retrospective                                    | Chen et al.                                    |
| Carbapenem treatment combination therapy        | Retrospective                                    | Kaya Kilic et al.                              |
Table 3. Clinical management of myelosuppression according to severity grading

| Severity grade | Grade 1 mild | Grade 2 moderate | Grade 3 severe | Grade 4 life-threatening |
|----------------|--------------|------------------|----------------|-------------------------|
| Anemia         | 9.5–10.5 g/dL | 8.0–9.4 g/dL     | 6.5–7.9 g/dL   | <6.5 g/dL               |
| Platelet (/mm³) | 75,000–99,999 | 50,000–74,999    | 20,000–49,000  | <20,000                 |
| White blood cell (/mm³) | 3,000 to <LLN | 2,000 to <3,000  | 1,000 to <2,000 | <1,000                  |
| Absolute neutrophil count (/mm³) | 1,000–1,500 | 750–999         | 500–749        | <500                    |

Action
- Monitor carefully, and consider reduction of linezolid dose (300 mg daily or 600 mg thrice weekly)
- Monitor carefully, and consider reduction of linezolid dose (300 mg daily or 600 mg thrice weekly): in case of grade 2 neutropenia, stop linezolid immediately. In case of grade 2 anemia, consider eritropoietin. Restart at reduced dose once toxicity has decreased to grade 1
- Stop linezolid immediately. In case of grade 3 anemia, consider eritropoietin. Restart at reduced dose once toxicity has decreased to grade 1
- Stop linezolid immediately. Consider transfusion or eritropoietin. Restart at reduced dose once toxicity has decreased to grade 1

LLN: lower limit of normal.
treatment should be managed immediately to relieve suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality.

Clinical Management of Myelosuppression According to Severity Grading

The clinician should make reasonable judgments whether to continue, reduce, or stop linezolid if myelosuppression occurs. The risks and benefits of continuing linezolid should be considered carefully in this situation. The EndTB Consortium recommends clinical management of myelosuppression according to severity grading (Table 3).

There are no firm guidelines on how to re-administer linezolid after stopping the drug. However, several previous studies have recommended how to re-administer linezolid. A Nix-TB study used linezolid at 1,200 mg per day as the initial dose. According to the protocol, dose reduction to 600 mg daily and 300 mg daily or temporary cessation of linezolid is permitted.

Cattaneo et al. have recommended therapeutic drug monitoring (TDM) of linezolid to maintain an AUC/MIC ratio of 100 and adjust the linezolid dose. The linezolid dose has been reduced to less than 300 mg/day without compromising efficacy. A dose reduction to 200 or even 150 mg of linezolid once daily can be considered when the AUC/MIC ratio is sufficiently high. For patients who develop dose-dependent toxicity, TDM should be considered to reduce linezolid doses on re-administration.

Conclusion

Linezolid is a promising option for treating MDR-TB and XDR-TB. However, hematologic toxicity is the major concern with a linezolid-containing regimen. Several clinical factors are considered as risk factors for its hematologic toxicity. Linezolid can block mitochondrial protein biosynthesis, reduce ATP production in bone marrow precursor cells, and cause myelosuppression. Increased sensitivity to linezolid in mitochondrial ribosomes might be associated with genetic variation in human mitochondria. Further studies are needed to address how to identify patients who will develop myelosuppression. Such studies should begin by identifying potential biomarkers of mitochondrial dysfunction and genetic susceptibility to predict myelosuppression. In the future, it will be necessary to evaluate whether adjusting the concentration of linezolid in the serum to obtain the pharmacodynamic target is a reasonable strategy to avoid adverse events in patients receiving prolonged courses of linezolid.

Authors’ Contribution

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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