Hematologic Side Effects Analysis of Linezolid in Mdr-TB Patients With Individual Therapy

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Background
In multidrug resistant tuberculosis (MDR-TB) therapy, Linezolid is included in group A, namely the drug that is prioritized to be administered together with dose 600 mg/day for 18-20 months and in combination with 3-4 other antibiotic (1,2). In general, linezolid has a good tolerance for short-term use, but side effects will arise with increasing use and increasing dose (3). Hematologic side effects are one of the most common to occur, characterized by anemia, leukopenia, and thrombocytopenia. The decline in the success rate of therapy is the effect of the drug resulting from discontinuation of therapy. The risk factors for side effects need to be known so that clinicians are more aware by increasing the monitoring of side effects. In Indonesia, there is no data on the prevalence of side effects of linezolid and there are no studies that examine the risk factors for side effects of linezolid in tuberculosis patients. The aim of this study was to see the prevalence of side effects and to identify risk factors for hematologic side effects due to linezolid.

Methods
It was using retrospective data of MDR-TB patients from January 1st 2018 to May 31th 2020 at tuberculosis outpatient unit in Dr. Soetomo Teaching Hospital Indonesia. All patients received individual regimen for MDR TB patients according to Indonesian Ministry of Health Guideline, the inclusion criteria in this study are patients with a diagnosis of adult MDR TB and had undergone a complete blood count at least 2 times. While the exclusion criteria is all conditions that could bias the hematologic measurements. Descriptive analysis was in the form of prevalence and onset of side effects. Statistical analysis was performed using the SPSS ver. 26 in the form of univariate and multivariate binary logistic regression tests on risk factors for hematologic side effects.

Result
There were 93 patients included in this study. The majority side effect experienced by patients was anemia with 27 cases (29.03%) with severity ranging from mild to life threatening. Thrombocytopenia occurred in 3 cases (3.22%), Leukopenia 2 cases (2.15%), the onset of side effects 91 days after starting linezolid therapy. The earliest onset of side effects was on day 12 and the longest appeared on day 243. The results of the binary logistic regression analysis showed that dose per kg per day (DPKD) with adjusted odd ratio of 5.509 (95% CI 1.51-20.2) was the only risk factor that affected the emergence of anemia side effects of linezolid.

Discussion
The prevalence of side effects was noted to be lower than other similar studies such as the study by Tang in China which showed that 51.5% (vs 29.03%) of MDR-TB patients on linezolid therapy were anemic. 12.1% (vs 3.22%) had thrombocytopenia, and 15.2% (vs 2.17%) had leukopenia (4). Lee said that 60% had anemia and 17.1% had leukopenia. The difference in results could be due to differences in patient characteristics, which resulted in different risk factors for exposure to side effects (5).

Risk Factor | Crude OR | P value | Adjusted OR (95% CI) | P Value
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Patients factor
Age | 2.122 | 0.292 | | |
Gender | 0.445 | 0.084 | | |
Creatinine Serum | 2.122 | 0.292 | | |
Creatinine Clearance | 2.358 | 0.113 | | |
Comorbid
Diabetes mellitus | 1.048 | 0.918 | | |
Coronary arterial disease | 1,000 | 1,000 | | |
Hypertension | 2,500 | 0.523 | | |
Stroke | 1,000 | 1,000 | | |
Drug factor
Dosage per kgBB per day | 4,237 | 0.015 | 5,509 (1.51-20.2) | 0.010
Hematological baseline
Baseline hemoglobin | 1,556 | 0.336 | | |
Baseline trombocyte | 5,200 | 0.186 | 12,1 (0.80-182,5) | 0.072

Body weight is affected by the distribution of water and fat in patients which will affect the volume of drug distribution (9). Linezolid has a protein drug binding of 30% and a distribution volume of 45-60 liters, linezolid structure of linezolid which tends to be polar causing high levels of free drugs in the blood and higher water solubility (10). Consequently, in patients with lower body weight, linezolid will have a higher area under curve (AUC) as well as plasma concentration so that there is more potential for side effects. These results suggest that linezolid dosing should be adjusted according to the patient’s body weight. Research related to the effectiveness and safety of linezolid conducted by Milliard showed that 300 mg / 12 hours was the optimal dose which shows the best level of effectiveness with minimal potential side effects so it can be considered as input as the next linezolid dosing scenario (11).

Conclusion
This study showed that the occurrence of linezolid hematological adverse effects in MDR TB patients were prevalent. We recommend to adjust dose of linezolid or to tighter hemoglobin monitoring in patients weighing <54.5 kg to prevent anemia from occurring and to increase awareness of anemia after 2 weeks of treatment.

References