Int J Clin Exp Med 2016;9(9):18554-18558
www.ijcem.com /ISSN:1940-5901/IJCEM0021546

Original Article

Clinical results of linezolid treatment for multidrug-resistant tuberculosis in china: cases report and literature review

Qingzhong Zeng[1], Jianqin Liang[2], Jinhe Wang[2], Lihong Wu[2], Zhi Chen[2], Shisheng Feng[2], Jingyang Liu[2], Weimin Zhou[1]

[1]*Department of Vascular Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, China;* [2]*Tuberculosis Research Institute, The 309th Hospital of Chinese PLA, Beijing 100091, China*

Received December 9, 2015; Accepted July 2, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: This study describes the clinical experience of linezolid (LZD) treatment of multidrug-resistant tuberculosis (MDR-TB). LZD-based chemotherapy was administered at 600 mg/d for 6 months as an intensive therapy, followed by 300 mg/d for at least 3 months. During treatment, chest computed tomography examination results, sputum smear acid-fast staining results, blood biochemistry and routine measures, and treatment adverse effects were recorded monthly. Patients with comorbidities or other potentially fatal diseases were excluded from this study. Of the 12 patients including 7 men and 5 women aged 21-58 years, and 3 completed the therapy and were considered cured. The others stopped treatment early because of adverse events (including acroanesthesia, insomnia, and palpitations) or TB relapse after 1-8 months. However, some patients showed improvement in clinical symptoms (mean, 18 days), cavity narrowing (45 days), and sputum-smear conversion (7-60 days). Therefore, oral administration of LZD is an effective treatment for patients with MDR-TB including relapse cases. However, monitoring for adverse events is recommended.

Keywords: Tuberculosis, multidrug-resistant tuberculosis, linezolid, efficacy, adverse event

Introduction

The World Health Organization (WHO) reported that there are approximately 490,000 cases of multidrug-resistant tuberculosis (MDR-TB) globally each year, accounting for 4.8% of the world's TB cases. Extensively drug resistant-TB (XDR-TB) represents 7% of MDR-TB cases [1, 2]. China is one of 27 countries with a high MDR-TB burden, with approximately 120,000 MDR-TB cases annually, corresponding to 1/3-1/4 of MDR-TB cases worldwide. MDR-TB treatment is associated with poor prognosis and high incidence of adverse reactions; therefore, effective anti-TB drugs are urgently needed to prevent MDR-TB.

Recent studies have reported good permeability of linezolid (LZD) in alveolar tissue and good efficacy in treatment of MDR-TB and XDR-TB [3-13]. In order to evaluate the effectiveness of LZD treatment in China, 12 patients with MDR-TB were administered LZD treatment and were followed-up.

Clinical information

MDR-TB cases were confirmed by positive sputum culture for mycobacterium tuberculosis (MTB) as well as positive sputum smears for acid-fast-bacillus (AFB), and resistance to isoniazid (H) and rifampicin (R). Patients with comorbidities or other potentially fatal diseases were excluded from this study. Seven men and 5 women aged 21-58 years (mean, 33 years) were included; 11 patients had recurrent TB and 1 was newly diagnosed with TB. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the 309th Hospital of Chinese PLA. Written informed consent was obtained from all participants.

Treatment

Patients underwent individualized chemotherapy according to medication history and drug-susceptibility testing. All patients received LZD

combined with 2 or 3 second-line anti-TB drugs. LZD was intravenously or orally administrated at a dose of 600 mg/d during the 6-month intensive therapy, followed by an oral dose of 300 mg/d for at least 3 months. During the treatment, clinical symptoms were checked daily; sputum culture for MTB, sputum AFB smears, chest computed tomography (CT), routine blood and urine examinations, coagulation index measurements, hepatorenal function evaluation, electrocardiography, and vision tests were performed monthly.

Therapeutic assessment

Imaging evaluation: 1) Focus assessment. Apparent absorption was defined as focus absorption to ≥1/2 primary lesion size; absorption as focus absorption <1/2 primary lesion size; invariance as no apparent focus change; and deterioration as focus expansion or dissemination. 2) Cavity evaluation. Closure was defined as closed or blocked cavities; narrow as cavity narrowing to ≥1/2 its original diameter; invariance as cavity narrowing or expanding to <1/2 original diameter; deterioration; and cavity expansion as >1/2 the original cavity diameter.

Bacteriological evaluation: Negative culture conversion was defined as negative sputum cultures for 2 consecutive months. Treatment outcomes were categorized into four groups according to WHO and Laserson criteria: success (cure or treatment completion), failure, default, or death [14, 15].

Results and follow-up

Only 3 of the 12 patients completed chemotherapy; they were cured without relapse at the 1-year follow-up, confirmed by negative sputum AFB smear, negative sputum MTB culture (BACTEC 960), and closed cavities on lung CT images. The other 9 patients had improvements in clinical symptoms, cavity narrowing, and sputum-culture conversion rates; however, 3 patients failed treatment, 2 for adverse events that could not be controlled with reduced LZD doses, resulting in discontinuation of therapy. One patient relapsed after 4 months. Patient progress is shown in **Table 1**.

Discussion

MDR-TB remains a challenge for global TB control because its treatment is long with low cure rates. For treatment of MDR-TB, only safe, well-tolerated second-line drugs or drugs with uncertain curative effects are used, based on drug susceptibility testing results and patient medication history [16]. However, these treatments are always less effective and more expensive. Therefore, new and effective anti-TB drugs are urgently needed. LZD, a newly synthesized oxazolidinone antibiotic can compete with mRNA to bind the bacterial 50S ribosomal subunit, thus preventing formation of the 70S initiation complex and suppress bacterial protein synthesis in the early stages of translation. *In vitro* and animal studies have confirmed the antibacterial activity of LZD against drug-resistant MTB [17]. The WHO currently classifies LZD as an anti-TB drug with uncertain efficacy.

In 1996, Zurenko et al [4] found that LZD showed anti-MTB activity *in vitro*. The minimum inhibitory concentration (MIC) against MTB isolates (including MDR-TB) was 0.5-2.0 μg/mL. The anti-bacterial activities against antibiotic-sensitive and resistant strains are the same for both exponential and stationary phases [18, 19]. In 2005, Fortun et al reported for the first time that 5 MDR-TB patients were cured with LZD combined with other drugs; their sputum culture conversion was observed 6 weeks after treatment [6]. In 2012, Sotgiu et al [12] reported that LZD was effective against MDR/XDR-TB, with a cure rate of 81.8%, a MTB smear conversion rate of 92.5% after 43.5 days, and MTB culture conversion of 93.5% after 61 days. Lee et al [14] studied LZD treatment of XDR-TB and reported an 89% sputum smear conversion rate after 6 months of therapy (34/38). Zhang et al [15] observed satisfactory therapeutic effects in 15 XDR-TB patients treated with LZD (81.8%, 9/11). Garcia-Prats et al [16] recommended a low dose of LZD to treat children with DR-TB.

Our findings suggest that LZD can significantly improve symptoms in patients with MDR-TB, promote cavity narrowing or closure, and prevent transmission of drug-resistant TB, but patients should be monitored for adverse events.

The U.S. Food and Drug Administration recommends that patients with Gram-positive bacterial infections receive 600 mg LZD twice daily. However, 12-24 months of such high doses for treatment of MDR-TB will unavoidably cause

Table 1. Treatment and outcomes in patients with MDR

No.	Chemotherapy	LZD 600 mg/d (month)	LZD 300 mg/d (month)	LZD application (month)	Improment in symptoms (day)	Cavity narrowing (month)	Cavity closure (month)	Sputum-smear conversion (day)	Sputum-culture conversion (day)	Outcome
1	LZD, D, Pto	9	0	9	30	1	5	21	21	Cure
2	LZD, Z, D, Pto	10	2	12	30	2	7	14	21	Cure
3	LZD, D, Pto, MFx	9	3	12	16	2	4	60	60	Cure
4	LZD, Z, D, Pto	6	2	8	23	2	3	7	21	Improvement
5	LZD, Z, D, Pto, A	1	0	1	24	No follow-up	No follow-up	No follow-up	No follow-up	Falure, interruption

serious adverse effects, consistent with foreign reports [4, 16, 20, 21]. Lee et al [14] reported an 87% incidence of adverse effects (33/38) during LZD treatment of XDR-TB, including 31 cases directly related to LZD. Migliori et al [9] reported 30 cases of hematopoietic disorders, 3 cases of neuritis, and 4 cases of gastrointestinal intolerance among 85 patients receiving LZD; 10 patients recovered after symptomatic therapy and continued treatment; however, 27 patients discontinued treatment due to adverse reactions. Among 24 patients receiving LZD, Koh et al [18] observed hematopoietic disorders in 1 patient and neuritis in 8 patients, which caused treatment withdrawal in 2 patients. Anger et al [19] reported that 81% of 16 patients with MDR-TB receiving LZD developed myelosuppression and gastrointestinal symptoms after 5-8 weeks; 44% had neuritis after 16 weeks and 31% discontinued treatment due to adverse reactions. Of 12 patients receiving 600 mg/d LZD in our study, the drug was withdrawn due to serious adverse events in 2 patients; this 33.33% incidence was lower than that observed in other literature reports [16, 21].

High doses of LZD can induce severe adverse events [10, 12, 22]. While lower doses may reduce the incidence of adverse reactions, administration of 600 mg per day can significantly improve symptoms in patients with MDR-TB and reduce sputum-smear conversion time, which was as good as a dose of 600 mg twice daily, but it would relieve the physical, psychological, and economic burden of patients and markedly reduce adverse effects. However, at least 9 months of treatment for MDR-TB are strongly recommended, with close monitoring for adverse reactions.

Globally, few patients with MDR-TB are treated with LZD, and its safety and efficacy have not been fully evaluated. We observed 12 patients with MDR-TB, including 7 patients still in treatment. To further clarify the efficacy of LZD for treatment of MDR-TB, large, multi-center, randomized controlled trials are required to collect some more clinical data and provide evidence for reasonable clinical decisions.

Disclosure of conflict of interest

None.

Address correspondence to: Weimin Zhou, Department of Vascular Surgery, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Nanchang 330006, China. Tel: +86 791 86298961; Fax: +86 791 86298961; E-mail: zhouweiminnc@126.com

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