Short Communication

Clinical Outcomes of Linezolid Treatment for Extensively Drug-Resistant Tuberculosis in Beijing, China: A Hospital-Based Retrospective Study

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SUMMARY: Studies have shown that linezolid achieves good clinical outcomes against multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB). However, the efficacy of linezolid for individual TB patients and its precise contribution to combination regimens remain unclear for Chinese patients. This study examined the clinical outcomes and safety of linezolid in adults with XDR pulmonary TB at the Chinese PLA 309 hospital. Sixteen XDR-TB patients received linezolid (600 mg daily) in addition to vitamin B6 (50–100 mg daily) as part of their individualized treatment regimens. Of the 16 patients, 14 had received previous treatment for tuberculosis. Sputum samples for all patients showed high colony-forming unit counts when tested by a real-time polymerase chain reaction (PCR). In addition, a high proportion of patients had cavitory lesions in the lungs. Eleven of the 16 patients (68.75%) had successfully completed therapy with documented negative quantitative PCR (qPCR) data and cultures at follow-up (mean = 12 months). Three patients (18.75%) are still receiving treatment, and all 3 have shown clinical and radiographic improvement. Linezolid was discontinued for 2 patients with persistent positive qPCR data and cultures because they developed severe, intractable diarrhea and nausea shortly after beginning treatment. Data indicated that linezolid was a well-tolerated and efficient treatment for XDR-TB in Chinese patients.

The recent increase in multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is an international public health threat. More than 90 countries have reported MDR-TB cases, and XDR-TB has been found in more than 60 countries. Especially high rates have been documented in India, Russia, South Africa, and some areas of the People's Republic of China (1). China has the second-largest number of TB cases in the world, and drug resistance is a serious public health issue due to the excessive use of second-line drugs. Therefore, new chemotherapeutic regimens are urgently needed to treat MDR-TB and XDR-TB cases in China.

Linezolid, the first oxazolidinone antibacterial agent that was approved for clinical use, has shown good clinical outcomes against TB in some studies, regardless of drug resistant patterns (2–4). However, its efficacy in individual TB patients and its precise contribution to combination regimens remain unclear in Chinese patients. Considering that the clinical efficacy of the antibiotic varied across geographical region, investigations that describe the clinical use of linezolid in China should be performed to explore whether linezolid may be effective in treating MDR- and XDR-TB in Chinese patients. In this study, we examined the clinical outcomes and safety of linezolid in adults with XDR pulmonary TB in the Chinese PLA 309 hospital, the

Chinese military's center for tuberculosis treatment and research.

Patients in this study (n = 16) were recruited by the Chinese PLA 309 hospital between January 2011 and December 2013. Background information for each patient (e.g., name, age, gender, birthplace, and medical treatment history) was recorded by their attending physicians when the patients were first hospitalized. None of the patients were HIV-infected. Those with delayed puberty were excluded from the study. Standard smears for acid-fast bacilli were performed with Ziehl-Neelsen staining, and mycobacterial cultures were conducted using Lowenstein-Jensen media. Phenotypic drug resistance was determined using Middlebrook 7H10 agar media supplemented with oleic acid, albumin, dextrose, and catalase. All patients were treated with linezolid and at least 3 other second-line companion drugs selected according to their individual drug history and recent susceptibility results. All patients received oral linezolid at a dosage of 600 mg daily. Treatment regimens also included vitamin B6 at a dosage of 50–100 mg daily to reduce the risk of hematologic toxicity.

At least 3 sputum samples were collected from each patient prior to and during the treatment period. Sputum samples were placed into 50 ml screw-cap centrifuge tubes and sent daily from the ward to the microbiology laboratory where the specimens were stored at 4°C until they could be processed. Colony-forming unit (CFU) counts were determined by a real-time polymerase chain reaction (PCR) assay [(Mycobacterium Tuberculosis Real Time PCR Kit (Liferiver Company, China)) and mycobacterial cultures as described in previous reports (5,6). CFU counts were conducted every week until negative results were found con-

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secutively for at least one month. A complete blood count, urinalysis, and serum aspartate aminotransferase were reviewed weekly to monitor for adverse events. And total bilirubin, creatinine, and glucose levels were similarly reviewed weekly.

Sixteen XDR patients (10 male; 6 female) between the ages of 19 and 60 years old with a body weight range of 45.5 to 82.5 kg were treated with linezolid. Of the 16 patients, 14 had a history of tuberculosis treatment. Sputum samples for all patients showed high CFU counts when tested by a real-time PCR, and there was a high proportion of patients with cavitory lesions in the lungs ($n = 12$; 75%). Table 1 shows the specific drugs used in each case. The median number of drugs used for these patients was 5. Drugs were chosen according to the drug susceptibility test results. Isoniazid, rifampicin, and ofloxacin were not used because all 16 XDR-TB cases showed resistant to these drugs. The mean duration of linezolid administration was 9.53 months (range 3–21 months).

As shown in Table 2, 11 of the 16 patients (68.75%) successfully completed therapy with documented negative qPCR data and cultures at follow up (mean follow-up 12 months; range 4–18 months). 3 patients (18.75%) are still receiving treatment; however, all 3 have shown clinical and radiographic improvement. The median time to qPCR or culture conversion among the 14 achieved conversion cases was 7.86 weeks. None of the 11 patients who successfully completed treatment, relapsed at follow-up.

Gastrointestinal adverse events occurred in 5 of the 16 patients. Linezolid use was suspended in 2 patients with persistent positive qPCR data or cultures because both of them developed severe, intractable diarrhea and nausea shortly after beginning linezolid. These cases were defined as treatment failure cases (12.5%). Hematological adverse events occurred in 6 patients. Four patients experienced mild-to-moderate anemia, and 2 patients developed mild thrombocytopenia.

However, none of these patients stopped the linezolid treatment. Peripheral neuropathy occurred in 3 patients; however, all 3 continued the linezolid treatment under careful monitoring. Lactic acidosis and serotonin syndrome, known side effects of linezolid (7,8), were not seen in our study.

Over the past 20 years, the TB morbidity rate has been declining worldwide. However, the disease is still considered one of the most fatal infectious diseases in developing countries (9). The XDR-TB patterns identified in a 2006 report (10), indicated that the pathogenic bacterium is susceptible to fewer than 3 classes of second-line drugs. This makes it difficult for treatment to meet international standards. In addition, patients with XDR-TB have a higher risk of death and treatment failure than those with MDR-TB. The northern and northeastern regions of China are adjacent to Russia and Mongolia, two countries with a high rate of XDR-TB (11,12). Given that Beijing, the political and financial center of China, is located in northern region of China, a high likelihood of XDR-TB transmission is possible. Therefore, new drug candidates should be recommended to recruit the anti-TB drug catalogue in this area.

Published clinical trials have demonstrated the efficacy of linezolid as part of an optimized MDR-TB or XDR-TB regimen; however several studies have also reported its inefficacy and side effect induced failures. For example, Lee et al. (4) reported that by 16 weeks, 63% of patients ($n = 12/19$) being treated with a linezolid containing regimen showed culture conversion in liquid medium and several clinically significant adverse events (e.g., myelosuppression, peripheral neuropathy, optic neuropathy, hepatic enzyme elevation, and rhabdomyolysis). Park et al. (13) reported successful culture conversion in 8 HIV-negative patients; however, even with a daily linezolid dose of 600 mg, the study described a high incidence of side effects indicating that linezolid may be effective but is poorly tolerat-

Table 1. Characteristics of patients and treatment data

Patient no.	Sex ¹⁾ and age at treatment initiation	Cavitory status at time of MDR-TB diagnosis	PCR results at time of MDR-TB diagnosis	culture results at time of MDR-TB diagnosis	Resistance pattern ²⁾ (in addition to INH, RMP and OLF resistance)	Drug regimen (in addition to LZD)	Treatment history
1	M, 54	+	10 ⁵	10 ⁵	EMB, PZA, AM	PAS, SM, CPM, CFZ	Yes
2	M, 22	–	10 ⁴	10 ⁴	SM, PZA, PAS, KN	EMB, AM, CFZ	No
3	F, 31	+	10 ⁴	10 ⁴	PAS, CPM	EMB, PZA, SM, AM	Yes
4	F, 33	+	10 ⁷	10 ⁷	EMB, PZA, AM	SM, CFZ, PAS, KN	Yes
5	M, 38	–	10 ³	10 ³	EMB, AM	SM, PZA, PAS	Yes
6	M, 19	–	10 ⁵	10 ⁵	EMB, SM, KN, CPM	PZA, PAS, AM, RFB	Yes
7	M, 41	+	10 ⁴	10 ⁴	SM, PAS, KN,	MFx, EMB, PZA, AM	No
8	F, 42	+	10 ⁷	10 ⁷	EMB, PZA, PAS, KN	SM, RFB, AM, CFZ	Yes
9	M, 52	+	10 ⁸	10 ⁸	SM, PZA, PAS, AM	EMB, MFx, RFB, KN	Yes
10	F, 46	+	10 ⁵	10 ⁵	EMB, PAS, AM	SM, PZA, MFx	Yes
11	M, 46	–	10 ³	10 ³	SM, AM	EMB, PZA, PAS, MFx	Yes
12	M, 39	+	10 ⁵	10 ⁵	PZA, AM	SM, EMB, PAS, MFx	Yes
13	F, 40	+	10 ⁶	10 ⁶	EMB, PZA, SM, AM	PAS, CFZ, RFB	Yes
14	F, 39	+	10 ⁴	10 ⁴	SM, AM, KN	EMB, PZA, PAS, CPM	Yes
15	M, 51	+	10 ⁵	10 ⁵	SM, PZA, KN	EMB, PAS, MFx, CPM	Yes
16	M, 53	+	10 ⁴	10 ⁴	SM, EMB, CPM	MFx, AM, PAS	Yes

¹⁾: M, male; F, female.

²⁾: EMB, ethambutol; SM, streptomycin; PZA, pyrazinamide; PAS, para-amino salicylic acid; AM, amikacin; KN, kanamycin; CPM, capreomycin; RFB, rifabutin; MFx, moxifloxacin; CFZ, clofazimine; INH, isoniazid; RMP, rifampicin; OLF, ofloxacin; LZD, linezolid.

Table 2. Treatment outcomes and toxicities

Patients no.	Period from start of treatment to culture conversion, week	Duration of linezolid therapy, month	Reported toxicity	Reason for discontinuing linezolid	Treatment outcome
1	9	21	None	COT ¹⁾	Cure
2	7	20	None	COT	Cure
3	9	17	None	COT	Cure
4	13	16	None	COT	Cure
5	4	8	None	COT	Continue treatment
6	8	6	None	COT	Cure
7	6	9	None	COT	Cure
8	12	8	None	COT	Cure
9	8	4	Severe diarrhea, nausea	Severe diarrhea, nausea	Continued treatment with other strategy
10	8	6	None	COT	Cure
11	4	8	None	COT	Cure
12	Positive	3	None	(-)	Continued treatment
13	7	4	Severe diarrhea, nausea	Severe diarrhea, nausea	Continued treatment with other strategy
14	Positive	3	None	(-)	Continued treatment
15	7	11	None	COT	Cure
16	8	9	None	COT	Cure

¹⁾: completion of treatment.

ed. Similarly, Fortun et al. (14) described the successful linezolid treatment for 5 patients with MDR-TB; however, 4 patients receiving 600 mg of oral linezolid, twice daily developed severe anemia requiring blood transfusion. In contrast, Schecter et al. (3) presented their findings for 30 MDR-TB patients who received linezolid treatment and showed that the linezolid was well tolerated with low rates of discontinuation and high efficacy. To the best of our knowledge, in China, only Xu et al. (15) reported clinical data regarding the treatment of 18 MDR-TB patients (including 15 XDR-TB cases) with linezolid. However, the authors note that the small sample size and geographical isolation limit the generalizability of their results. Our previous studies conducted at the PLA 309 hospital have shown that linezolid demonstrates good in vitro activity against XDR-TB strains isolated from patients with MIC values of 2 mg/L or lower (16). Here we present findings from our clinical investigation regarding the use of linezolid treatment for XDR-TB. Our case series is the first report from northern China concerning the use of linezolid-containing regimens for the treatment of XDR-TB. The initial dose of linezolid used here was 600 mg once daily; a dose lower than that used by Xu et al. (1,200 mg divided into 2 doses). The FDA-approved dose for gram-positive organisms (1,200 mg daily) is used in most anti-TB case series, however, several reports indicated that a half dose might also be effective and induce lower toxicity (3,4). Our data indicated a high proportion of successfully completed therapy and a low rate of side effects. The main side effects in our cohort were severe diarrhea and nausea, mild-to-moderate anemia, and peripheral neuropathy. No patients reported lactic acidosis or serotonin syndrome. These results are similar those reported by Schecter et al. (3) but contradict those reported by Xu et al. (15). This indicates that a dosage of 600 mg/day might be suitable for Chinese XDR patients. Furthermore, the addition of vitamin B6 might be responsible for the low occurrence

of side effects. Vitamin B6 is required for the synthesis of d-aminolevulinic acid, a precursor of heme synthesis, and a deficiency may cause normocytic, microcytic, or megaloblastic anemia. In addition, previous studies have demonstrated that the intake of vitamin B6 might decrease hematologic toxicity (3). In this study, all patients received vitamin B6 as part of their treatment regimen. Although 6 patients experienced mild-to-moderate anemia and thrombocytopenia, no patients terminated the linezolid treatment because of myelosuppression.

The small sample size in this study limits its generalizability. Furthermore, although the results are encouraging and few treatment failures and cases of acquired resistance were reported, we cannot conclude that linezolid is suitable for all XDR-TB patients in China. Although we recommend the use of linezolid, patients must be closely monitored for any adverse side effects. Furthermore, linezolid TB treatment guidelines are necessary.

Conflict of interest None to declare.

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