# Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

Shenjie Tang[1,2,8], Lan Yao[2,8], Xiaohui Hao[2,8], Xia Zhang[3], Gang Liu[4], Xin Liu[5], Meiying Wu[6], Linhai Zen[2], Hua Sun[7], Yidian Liu[2], Jin Gu[2], Feishen Lin[3], Xiafang Wang[6] and Zhanjun Zhang[2]

**Affiliations**:
[1]Tuberculosis Multidisciplinary Center for Diagnosis and Treatment, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumour Research Institute, Beijing, China.
[2]Tuberculosis Center for Diagnosis and Treatment, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.
[3]Nanjing Chest Hospital, Nanjing, China.
[4]Anhui Chest Hospital, Hefei, China.
[5]Henan Chest Hospital, Zhengzhou, China.
[6]Souzhou Fifth People's Hospital, Souzhou, China.
[7]Shanghai Minhang Center for Disease Control and Prevention, Shanghai, China.
[8]Authors contributed equally.

**Correspondence**: Shenjie Tang, Tuberculosis Multidisciplinary Center for Diagnosis and Treatment, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Machang NO.97, TongZhou district, Beijing, 101149, China. E-mail: tangsj1106@hotmail.com

ABSTRACT Linezolid may be effective in treating multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. We conducted a prospective, multicentre, randomised study to further evaluate the efficacy, safety and tolerability of linezolid in patients with extensively drug-resistant tuberculosis in China.

65 patients who had culture-positive sputum for extensively drug-resistant tuberculosis were randomly assigned to a linezolid therapy group or a control group. Patients in the two groups adopted a 2-year individually based chemotherapy regimen. The linezolid therapy group was given linezolid at a start dose of 1200 mg per day for a period of 4–6 weeks and this was then followed by a dose of 300–600 mg per day.

The proportion of sputum culture conversions 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 linezolid therapy group was 69.7%, significantly higher than that in the control group (34.4%, p=0.004). 27 (81.8%) patients had clinically significant adverse events in the linezolid group, of whom 25 (93%) patients had events that were possibly or probably related to linezolid. Most adverse events resolved after reducing the dosage of linezolid or temporarily discontinuing linezolid.

Linezolid containing chemotherapy for treatment of extensively drug-resistant tuberculosis may significantly promote cavity closure, increase sputum culture-conversion rate and improve treatment success rate.

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**Prospective, multicentre, randomised study evaluating efficacy, safety and tolerability of linezolid in XDR-TB** http://ow.ly/ztVfd

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## Introduction

An increasing incidence of extensively drug-resistant tuberculosis (XDR-TB) is a major concern for tuberculosis (TB) control programmes worldwide [1, 2]. XDR-TB is defined as TB with *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone (*e.g.* ofloxacin or levofloxacin) and at least one of the injectable drugs (amikacin, capreomycin or kanamycin) [3, 4]. According to the World Health Organization (WHO) there were an estimated 450 000 new cases of MDR-TB globally in 2012 [5]. XDR-TB had been reported by 92 countries by the end of 2012 [5]. China is one of the world's 22 countries with the highest *per capita* burden of tuberculosis and is one of the world's 27 countries with the highest burden of multidrug-resistant TB (MDR-TB)/XDR-TB. The prevalence of XDR-TB is of very serious concern in China [1, 6–8]. The treatment of patients with XDR-TB is more difficult, toxic and costly. Because of the lack of efficacious anti-TB drugs, the treatment is also less effective than that of other forms of TB so that XDR-TB is frequently fatal [9–11].

Studies *in vitro* have shown good activity of linezolid against various species of mycobacteria, including drug-resistant mycobacterial strains [12–14]. Recent case studies and retrospective analysis have suggested that linezolid may be effective in treating MDR-TB and XDR-TB [15–22]. However, serious adverse events have been documented if linezolid is used for more than two weeks in spite of its good efficacy [23, 24]. Moreover, these studies all have major limitations including small numbers of patients, lack of control patients, and limited long-term follow-up and retrospective analysis. For this reason, we conducted a prospective, multicentre, randomised study to further evaluate the efficacy, safety and tolerability of linezolid in patients with XDR-TB in China.

## Methods

### *Study patients*

From October 2009 to August 2011, we enrolled patients aged between 18 and 64 years who had positive sputum cultures with an XDR strain and were continuously smear positive after using available chemotherapeutic options during the previous $\geqslant$12 months. All patients are tested for HIV and HIV-positive patients were transferred to HIV specialised hospitals immediately in China. Exclusion criteria included: 1) allergic to linezolid; 2) severe cardiovascular, liver, kidney or blood system disease or other serious illnesses; 3) mentally ill; 4) pregnant or lactating females; 5) a positive HIV test result; and 6) unable to purchase linezolid for economic reasons.

### *Study design*

This multicentre, prospective, randomised, controlled study was conducted in five large-scale TB specialised hospitals in China. Patients were randomly assigned to either a linezolid therapy group or a control group. Patients were then assigned to a 2 years of individually based chemotherapy regimens based on medication history and drug susceptibility tests (DST) results as recommended by WHO [3, 4]. Each regimen contained at least five drugs. Drugs were selected according to the five groups of anti-TB drugs recommended by WHO [3, 4]. The linezolid therapy group were given a start dose of 1200 mg linezolid per day for 4–6 weeks, after which they continued taking linezolid at a dose of 300–600 mg per day in accordance with body weight and tolerability. This continued until the patients provided two consecutive negative sputum cultures during a 2-month period (taken at least 30 days apart). According to previous studies, adverse events related to linezolid include anaemia, leukopenia and peripheral neuropathy. Severe adverse events was defined as haemoglobin <60 $g{\cdot}L^{-1}$, leukocytes <2000 $mm^{-3}$ or the symptoms that marked limitation in activity or intervention/therapy required or hospitalisations possible. If adverse events occurred, which were considered to be related to linezolid, the dose of linezolid would be reduced to 300–600 mg per day. The primary end-point was sputum-culture conversion. Conversion was considered when two consecutive cultures, taken at least 30 days apart, were found to be negative. Each patient was given directly observed therapy (DOT) throughout the treatment. DOT was carried out by trained supervisors in the communities.

The study was approved by The Ethics Committees of the five large-scale TB specialised hospitals. Individual participants gave written informed consent before enrolment in the study. The trial was performed in accordance with the Guideline For Good Clinical Practice [25] and was monitored by an independent data and safety monitoring committee. All the patients' information was routinely collected and recorded by attending physicians. All authors of this report are fully responsible for the study design, data collection, analysis, completeness of data reporting, and interpretation of the data.

### *Study procedures*

#### *Microbiological assessments and outcome measures*

Morning sputum specimens were obtained at least once every 3 months during the treatment period. However, sputa were collected at least once every 1 month before sputum culture conversion. Sputum


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samples were routinely tested by smear on fluorescence microscopy and by culture on Lowenstein-Jensen medium and in the BACTEC MGIT 960 system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). DSTs, which include the seven drugs streptomycin, isoniazid, rifampin, ethambutol, ofloxacin, amikacin and capreomycin, were performed on positive cultures by means of the MGIT 960 System according to the WHO guidelines [24]. All the tests were performed at the TB reference laboratory and quality control was routinely performed [26].

Treatment outcomes were defined according to the WHO and IUATLD (International Union Against Tuberculosis and Lung Disease) guidelines [3, 4, 27]. "Cured" was defined as a patient who had completed treatment according to programme protocol and had provided consistently negative cultures (with at least five results) for the final 12 months of treatment for TB. "Completed treatment" was defined as a patient who had completed the treatment according to the programme protocol but did not meet the definition for cured, because of lack of bacteriological results. The "died" category included any patient who had died, for any reason, during the course of the TB treatment. "Treatment failure" included any patient for whom two or more of the five cultures recorded in the final 12 m of therapy were positive, or if any one of the final three cultures was positive. "Defaulted" was defined as a patient whose TB treatment was interrupted for $\geqslant$2 consecutive months for any reason. Additionally, cured and completed treatment categories were combined as "treatment success", whereas others were combined as "poor treatment outcome".

### *Imaging evaluation*

Chest radiographs and computed tomography images were obtained at least once every 3 months during the treatment period. All images were evaluated by two physicians and a radiologist.

### *Safety assessments*

Patients underwent baseline and serial safety evaluations on a weekly basis until the linezolid was reduced at 4–6 weeks, after which it was undertaken every 2 weeks until the linezolid was stopped and then it was once a month. Leukopenia was defined as having a white blood cell count $<4.0\times10^9$ $L^{-1}$. Mild anaemia was defined as having haemoglobin in the range of 9–12 $g{\cdot}dL^{-1}$. Moderate anaemia was defined as having haemoglobin in the range of 6–9 $g{\cdot}dL^{-1}$. Severe anaemia was defined as haemoglobin <6 $g{\cdot}dL^{-1}$. A physician evaluated all patients by nerve-conduction studies at entry and a neurologist was consulted if any peripheral neuropathy developed. To monitor patients for linezolid-induced optic neuropathy, the study staff performed testing for visual acuity and colour vision. Adverse events were recorded daily and immediately reportable events and clinically significant abnormal laboratory results were evaluated as appropriate.

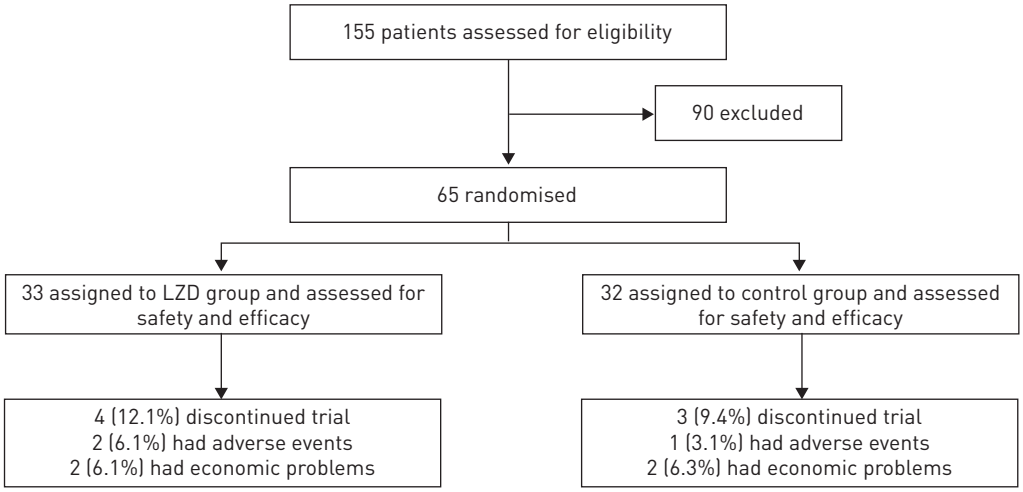


FIGURE 1 Enrolment, study-drug assignments, follow-up and assessment of patients. Between October 2009 and May 2011 a total of 155 patients were assessed for eligibility and 65 underwent randomisation. 33 patients were included in the linezolid (LZD) therapy group and 32 patients were included in the control group. Four patients in the linezolid therapy group discontinued the trial (two had adverse events and two due to economic factors) while three patients in the control group discontinued the trial (one had adverse events and two left due to economic factors).

### *Statistical analysis*

All statistical analyses were performed using SPSS14.0 software, version 14.0 (SPSS Inc., Chicago, IL, USA). Comparisons of categorical variables were performed using the Pearson Chi-squared tests or Fisher's exact tests to compare different groups. Statistical significance was set at $p<0.05$.

## Results

### *Study patients*

A total number of 155 patients with XDR-TB were assessed for eligibility. 90 patients were not able to attend the study. 30 patients did not meet the inclusion criteria (14 excluded because of respiratory failure; five excluded because of severe heart failure; one excluded because of severe hyperglycaemia; four excluded because of blood disease; five excluded because of liver injury; one excluded because of kidney disease). 60 patients were declined to participate in the study because they could not afford the cost of linezolid treatment. 65 patients were assigned treatment at random, with 33 assigned to the linezolid therapy group and 32 to the control group (fig 1). Mean age was 44 years, and no significant differences in demographic or baseline clinical characteristics between the two groups were identified (table 1). 100% of the patients had lung cavities. All patients had received anti-TB treatment for >1 year before their admission to the study. In the linezolid therapy group, the longest period of treating with linezolid was up to 24 months, the minimum was 2 months with an average of ~12 months. Four patients from the linezolid group discontinued therapy because of adverse effects (one at the second week and one at the fourth week) and economic problems (one at the fourth week and one at the second month). Three patients in the control

TABLE 1 General characteristics of the two groups[#]

| Characteristics | Linezolid therapy group | Control group | Total |
|---|---|---|---|
| **Subjects n** | 33 | 32 | 65 |
| **Age years** | 44 (18–64) | 43 (18–63) | 44 (18–64) |
| **Male sex** | 22 (66.7) | 21 (65.6) | 43 (66.2) |
| **Body mass index kg·m$^{-2}$** | 19.5 (12–30) | 19.6 (12–30) | 19.5 (12–30) |
| **With comorbidity** | | | |
| Diabetes | 6 (18.2) | 6 (18.8) | 12 (18.5) |
| Chronic obstructive pulmonary disease | 3 (9.1) | 4 (12.5) | 7 (10.8) |
| Bronchiectasis | 8 (24.2) | 9 (28.1) | 17 (26.2) |
| Tuberculous pleurisy | 6 (18.2) | 5 (15.6) | 11 (16.9) |
| Respiratory failure[¶] | 7 (21.2) | 6 (18.8) | 13 (20) |
| **Decreased albumin** | 10 (30.3) | 9 (28.1) | 19 (29.2) |
| **Lung cavities** | | | |
| Unilateral | 16 (48.5) | 15 (46.9) | 31 (47.7) |
| Bilateral | 17 (51.5) | 17 (53.1) | 34 (52.3) |
| **Course of disease** | | | |
| ⩾1 year <5 years before randomisation | 19 (57.6) | 18 (56.2) | 37 (56.9) |
| ⩾5 years before randomisation | 14 (42.4) | 14 (43.8) | 28 (43.1) |
| **Previous treatment** | | | |
| ⩾1 year <5 years before randomisation | 21 (66.7) | 22 (68.7) | 38 (67.7) |
| ⩾5 years before randomisation | 11 (33.3) | 10 (31.3) | 21 (32.3) |
| **Susceptibility test results resistance** | | | |
| Streptomycin | 30 (90.9) | 30 (93.8) | 60 (92.3) |
| Isoniazid | 33 (100) | 32 (100) | 65 (100) |
| Rifampin | 33 (100) | 32 (100) | 65 (100) |
| Ethambutol | 29 (87.9) | 30 (93.8) | 59 (90.8) |
| Ofloxacin | 33 (100) | 32 (100) | 65 (100) |
| Amikacin | 26 (78.8) | 25 (78.1) | 51 (78.5) |
| Capreomycin | 25 (75.8) | 25 (78.1) | 50 (76.9) |
| **Background regimen** | | | |
| Prothionamide, pyrazinamide, moxifloxacin or gatifloxacin or levofloxacin, para-aminosalicylic acid | 33 (100) | 32 (100) | 65 (100) |
| Capreomycin or amikacin | 18 (54.5) | 17 (53.1) | 35 (53.8) |
| Clofazamine | 22 (66.7) | 20 (59.4) | 42 (64.6) |
| Clarithromycin | 18 (54.5) | 19 (51.5) | 37 (56.9) |

Data are presented as n (%) or mean (minimum–maximum), unless otherwise stated. [#]: there were no significant between-group differences; [¶]: respiratory failure was defined as arterial oxygen tension lower than 60 mmHg by arterial blood gas analysis.


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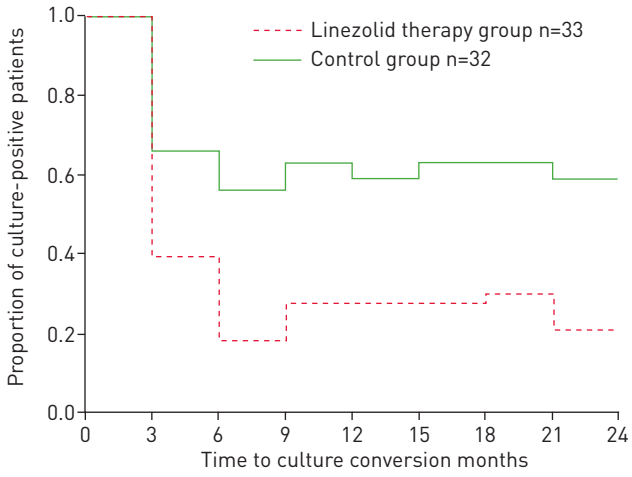


FIGURE 2 The proportion of patients with a positive sputum culture and the time taken for conversion to a negative culture in sputum.

group discontinued therapy, one because of adverse effects (at the third month) and two for economic problems (one at the fourth month and one at the fifth month).

### *Sputum conversion*

The proportion of sputum-culture conversion in the linezolid therapy group by culture in the BACTEC MGIT 960 system was 78.8% by 24 months, significantly higher than that in the control group (37.6%, $p<0.001$) (fig. 2).

### *Cavity closure*

The cavity closure rates in the linezolid group were 72.7%, 60.6%, 66.7%, and 69.7% by the end of the sixth, twelfth, eighteenth, and twenty-fourth months, respectively. These were significantly higher than those of the control group ($p<0.05$) (fig. 3). Representative radiologic findings for a 52-year-old male with XDR-TB were followed from the beginning of the linezolid treatment to the ninth month of treatment (fig. 4).

### *Treatment outcomes*

The treatment success rate in the linezolid therapy group was 69.7%, significantly higher than that in control group (34.4%, $p=0.004$) (table 2). Two patients in the linezolid therapy group died, one of whom died of a massive haemoptysis, while the other died from respiratory failure. Meanwhile, two patients in the control group died of respiratory failure, and one patient died from a massive haemoptysis.

### *Safety*

27 (81.8%) patients had clinically significant adverse events in the linezolid therapy group, of whom 25 patients (93%) had events that were possibly or probably related to linezolid (table 3). Most adverse events

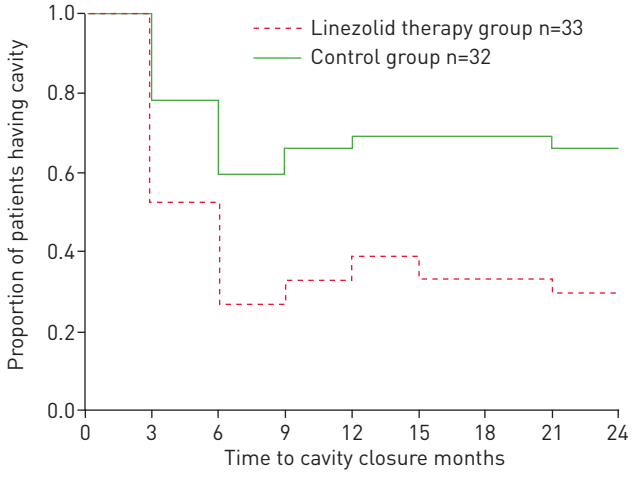


FIGURE 3 The proportion of patients having a cavity and the time to cavity closure.

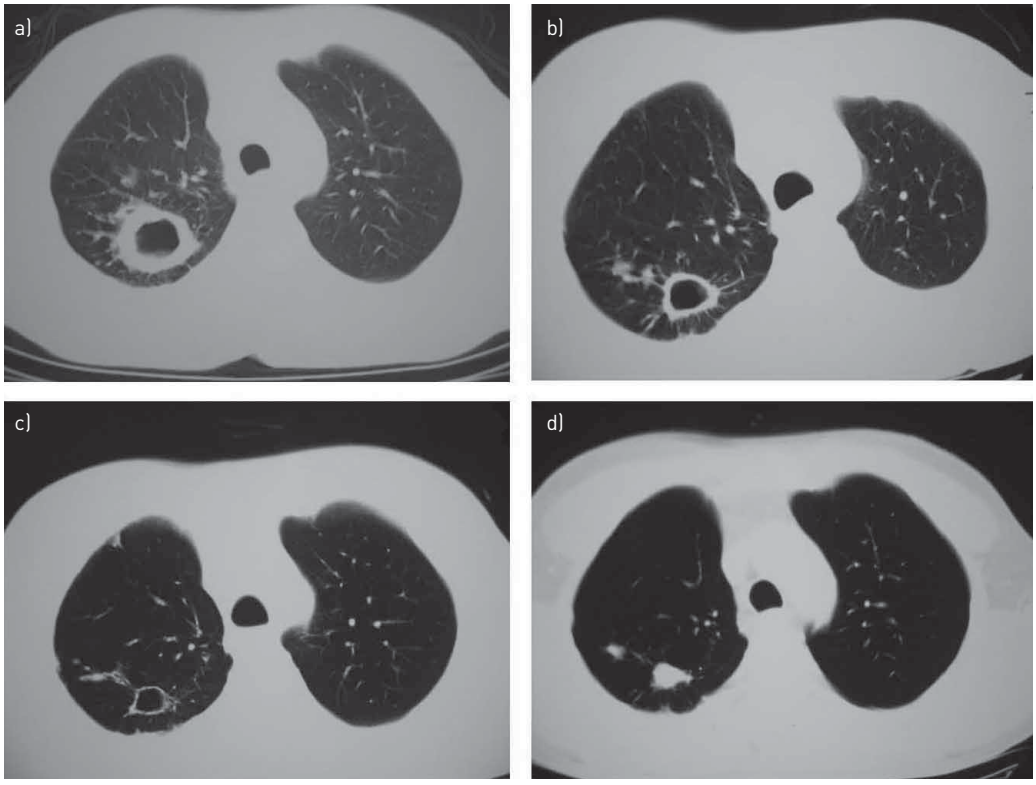


FIGURE 4 Computed tomography images of the chest in a 52-year-old male with extensively drug-resistant tuberculosis (XDR-TB). The radiologic findings of the male were followed from the beginning of the linezolid treatment to the ninth month of the treatment. He was diagnosed with pulmonary TB 5 years ago; with a cough, sputum expectoration, fever, and haemoptysis. After the diagnosis, he was given various kinds of anti-TB drugs. However, the symptoms were not relieved and the sputum smears remained positive. The sputum culture and drug susceptibility tests confirmed XDR/multidrug-resistant TB by BACTEC MIGT 960 (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). He was randomly enrolled to the linezolid therapy group. His anti-TB treatment regimen consisted of: 6 months capreomycin, para-aminosalicylic acid, prothionamide, pyrazinamide, levofloxacin, and clarithromycin; 18 months para-aminosalicylic acid, prothionamide, pyrazinamide, levofloxacin, and clarithromycin. A cavity of 4.0 cm × 4.2 cm was observed in the right upper lobe of the lung prior to the study (a). After 3 months of the treatment the sputum smear and the culture converted to negative, and the cavity shrank to 3.0 cm × 2.6 cm (b). In the sixth month of the treatment the sputum smear and culture remained negative and the cavity continued to shrink to the size of 1.9 cm × 1.8 cm (c). In the ninth month of treatment the sputum smear and culture remained negative, and the cavity closed (d).

resolved after reducing the dosage of linezolid or temporarily discontinuing linezolid, and only two patients were permanently discontinued from using the drug because of severe anaemia. The rates of anaemia, nausea/vomiting, optic neuropathy and peripheral neuropathy were 51.5%, 48.5%, 24.2% and 18.2% respectively in the linezolid therapy group, higher than those in the control group ($p<0.05$). We observed that haematological adverse reactions including anaemia, thrombocytopenia and leukopenia occurred between 2 weeks and 2 months after starting linezolid treatment. Gastrointestinal adverse reactions including nausea or vomiting occurred between 2 weeks and 4 weeks. In addition, we observed that peripheral neuropathy occurred between 2 months and 4 months, while optic neuropathy occurred later and usually around 5–6 months (fig. 5).

## Discussion

Linezolid is classified by the WHO as one of the group five drugs in DR-TB treatment [3, 4]. A series of studies evaluated the efficacy, safety and tolerability of the linezolid containing regimes for treating MDR- and XDR-TB cases. However, most were restricted mainly to case reports, a retrospective analysis and small case series [14–19, 28–31]. This is a prospective, multicentre, randomised study on efficacy, safety and tolerability of linezolid for treating XDR-TB. Our study included 65 patients with "intractable" XDR-TB who had not had a satisfactory response to previous long-term treatment with second-line drugs for a period of ⩾1 year and who all had extensive radiographic findings complicated by cavities. We found that the proportion of sputum-culture conversion in the linezolid group was 78.8% by 24 months, significantly higher than that in the control group (37.6%, $p<0.001$). The cavity closure rate in the linezolid group was 69.7% by the end of the twenty-fourth month, significantly higher than that of the


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TABLE 2 Treatment outcomes for the linezolid therapy group and the control group

| Treatment outcomes | Linezolid group | Control group | Chi-squared | p-value |
|---|---|---|---|---|
| **Patients n** | 33 | 32 | | |
| **Treatment success** | 23 (69.7) | 11 (34.4) | 8.125 | 0.004 |
| Cure | 17 (51.5) | 7 (21.9) | 6.128 | 0.013 |
| Treatment completion | 6 (18.2) | 4 (12.5) | 0.403 | 0.526 |
| **Poor treatment outcomes** | 10 (30.3) | 21 (65.6) | 8.125 | 0.004 |
| Death | 2 (6.1) | 3 (9.4) | 0.247 | 0.619 |
| Failure | 4 (12.1) | 15 (46.9) | 9.486 | 0.002 |
| Default | 4 (12.1) | 3 (9.1) | 0.126 | 0.723 |

Data are presented as n (%) unless otherwise stated.

control group ($p<0.05$). Furthermore, 23 (69.7%) patients in the linezolid therapy group had treatment success (cured and treatment completion), significantly more than those in the control group ($p=0.004$). These findings are in line with the results from previous studies [14–19, 22, 28–31]. Therefore, there is no doubt that regimens containing linezolid showed excellent efficacy in treating MDR/XDR-TB. Also we found that linezolid accelerated the cavity closure rate and sputum culture conversion rate. As early as 3 months after treatment, linezolid group had a higher cavity closure rate (48.5%, $p=0.025$) and sputum culture conversion rate (60.6%, $p=0.034$). It is very meaningful in controlling the spread of XDR-TB especially in developing countries. Early sputum culture conversion means fewer contagious risks for people contacting with those patients [23].

There is no unanimous opinion on either linezolid dose or duration of exposure to linezolid-containing regimens; there is insufficient evidence. Migliori *et al.* [28] performed a retrospective, nonrandomised, unblinded observational study evaluating the safety and tolerability of linezolid at 600 mg once daily or twice a day. in MDR/XDR-TB treatment in four European countries. Out of 195 MDR/XDR-TB patients, 85 were treated with a linezolid containing regimen for a mean of 221 days. Of these, 35 (41.2%) experienced major side-effects attributed to linezolid, requiring discontinuation in 27 (77%) cases. Recently, Koh *et al.* [32] adopted linezolid (300 mg per day) for treatment of 24 cases of MDR/XDR-TB. The average treatment time was 359 days. The results showed sputum conversion in 22 cases (92%) after using linezolid for an average of 89 days, and adverse reactions were significantly reduced, particularly neurotoxicity. In our study, linezolid was started at a dose of 1200 mg per day for 4–6 week, followed by 300 to 600 mg per day. The longest period of applying linezolid for treatment was up to 24 months and the minimum was 6 months with the average of ~12 months. Only two cases stopped the linezolid treatment because of severe anaemia in 2–3 weeks after 600 mg twice daily linezolid was initiated. In the first 4–6 weeks of the intensive phase using high-dose linezolid is aimed at exerting significant bactericidal activity for mycobacteria in logarithmic growth phase. In the continuous treatment phase the purpose of low-dose linezolid is to exhibit the long-term sterilising activity against the sporadically multiplying

TABLE 3 Adverse events of the linezolid therapy group and the control group

| | Linezolid group | Control group | Chi-squared | p-value |
|---|---|---|---|---|
| **Patients n** | 33 | 32 | | |
| **Anaemia** | 17 (51.5) | 2 (6.3) | 16.091 | 0.000 |
| **Thrombocytopenia** | 4 (12.1) | 1 (3.1) | 0.801 | 0.371 |
| **Leukopenia** | 5 (15.2) | 2 (6.3) | 0.573 | 0.449 |
| **Nausea/vomiting** | 16 (48.5) | 3 (9.4) | 12.013 | 0.001 |
| **Peripheral neuropathy** | 8 (24.2) | 1 (3.1) | 4.432 | 0.035 |
| **Optic neuropathy** | 6 (18.2) | 0 (0) | 4.424 | 0.035 |
| **Liver injury** | 6 (18.2) | 7 (21.9) | 0.138 | 0.710 |
| **Tinnitus or hearing loss** | 4 (12.1) | 5 (15.6) | 0.167 | 0.683 |
| **Rash or pruritus** | 3 (9.1) | 3 (9.4) | 0.002 | 0.968 |
| **Arrhythmia** | 3 (9.1) | 2 (6.3) | 0.185 | 0.667 |
| **Hypokalaemia** | 2 (6.1) | 2 (6.3) | 0.000 | 1 |

Data are presented as n (%) unless otherwise stated.

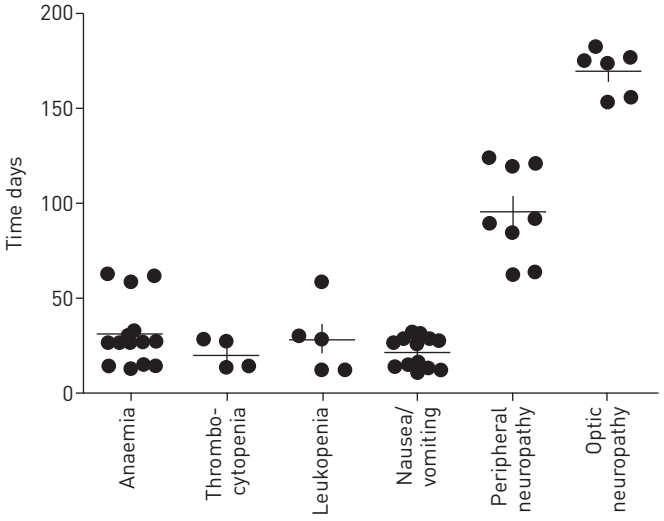


FIGURE 5 Time to linezolid related adverse events.

mycobacteria in stationary-phase growth [33]. Meanwhile, therapeutic drug monitoring (TDM) might reduce dose and adverse events of linezolid in the management of the drug dosage [34]. In another two studies linezolid was prescribed for the entire treatment duration, *e.g.* from 18.6 to 20.6 months [22, 35]. The most limiting problem related to the prolonged use of linezolid in MDR/XDR-TB is toxicity. We found that linezolid-related adverse events all occurred in the first 6 months of treatment and the long-term use of linezolid did not increase the incidence of adverse events or exacerbate former adverse events. Apart from the toxicity, another issue of the long-term use of linezolid is the high cost of the drug, and its use could be limited in many countries with high incidence of MDR/XDR -TB and low economic resources [16]. In our study, the majority of patients with XDR-TB who were eligible to participate in the trial were not enrolled because of the economic factor. In our setting, full treatment for MDR-TB/XDR-TB included free anti-TB drugs (prothionamide, pyrazinamide, moxifloxacin, gatifloxacin, levofloxacin, para-aminosalicylic acid, capreomycin, amikacin, clofazamine and clarithromycin) for all patients. Conversely linezolid can be added to such a regimen only if the patient can afford it and is randomly assigned in the linezolid group. This may cause "selection bias", but there was no significant difference between those who declined and those who took linezolid in terms of demographic, epidemiological, and clinical data.

The reported incidence of adverse reactions due to long-term application of linezolid is high [18, 19, 22]. Anger *et al.* [20] found that 13 of 16 cases had myelosuppression; the average lag time was 5 weeks after starting linezolid; 13 cases had gastrointestinal adverse reactions in an average of 8 weeks after starting linezolid treatment; seven cases had peripheral neuritis in an average of 18 weeks after starting. 11 patients improved after symptomatic treatment and reduction of linezolid dose, five cases finally stopped using linezolid. Males and the elderly were more vulnerable to generate neutropenia, thrombocytopenia and peripheral neuritis. Lee *et al.* [23] reported that of 38 patients with exposure to linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to linezolid and three patients discontinued therapy. Patients who received 300 mg per day after the second randomisation had fewer adverse events than those who continued taking 600 mg per day. According to a meta-analysis, about one out of every two patients experienced adverse events attributed to linezolid. The main adverse events were anaemia (38.1%) and peripheral neuropathy (47.1%); other haematological and non-haematological adverse events occurred in a lower proportion of cases (*i.e.* gastrointestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%) [24]. Our results showed that adverse events related to linezolid included gastrointestinal, haematological reactions, optic neuropathy and peripheral neuropathy. We are aware that despite the higher incidence of adverse reactions (and some of the reactions are serious), the overall drug programme would not be adversely affected by inclusion of linezolid as long as there is close observation and there are timely and correct interventions including discontinuation, reducing dosage of linezolid or blood transfusion *etc.* Haematological adverse reactions first occurred in the second to eight week after starting linezolid treatment; therefore, it is necessary to recheck blood and other indices weekly at the beginning. The onset of peripheral neuritis has been after 2–4 months of therapy, earlier than some reports [31]. Visual loss occurs later and usually around the fifth to sixth month of treatment. Not only the clinicians, but also the patients should be alert. We also found that previous adverse reactions were not aggravated, and new adverse events did not occur after half a year of linezolid treatment.


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Based on the available evidence and on the results of this study, linezolid seems to confirm its role as an important additional drug to be added in severe cases in specialised centres that are capable to manage its potential severe adverse events. The role of linezolid will be relevant until new regimens based on the new drugs now available (including delamanid and bedaquiline) will be introduced at the programmatic level [36–39].

Our study has several limitations. First, our study was limited by the relatively small number of patients with XDR-TB. Secondly, long-term follow-up of the treatment outcomes was not conducted in our study. Long-term clinical efficacy in these patients needs to be investigated to further understand recurrence rates. Thirdly, there is no evidence showing how many doses of linezolid are appropriate. We are also not sure whether there should be an intensive phase or a continuous phase or how long the treatment period with linezolid should be.

Despite these limitations, to our knowledge, this might be the first prospective, multicentre, randomised study on efficacy, safety and tolerability of linezolid for treating XDR-TB in China. Our study demonstrated that addition of linezolid to chemotherapy of XDR-TB can significantly accelerate cavity closure and sputum culture conversion, promote cavity closure rates and sputum culture conversion rate and improve treatment success rate. Therefore, linezolid could reduce spitting mycobacteria and the risk of contagiousness. Meanwhile, adverse reaction might be tolerated and resolved after suitable intervention. In conclusion, we suggest that linezolid be recommended for the treatment of XDR-TB.

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