International Journal of Infectious Diseases 118 (2022) 264–269

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Analysis of efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis

Jie Qiao[a,b,#], Lin Yang[d,#], Jing Feng[d], Xiyong Dai[c], Feng Xu[c], Ping Xia[a,*]

[a] Department of Orthopedics, The Central Hospital of Wuhan, Wuhan, China
[b] Hubei University of Chinese Medicine,Wuhan, China
[c] Department of Surgery, Wuhan Pulmonary Hospital, Wuhan, China
[d] Department of Orthopedics, Wuhan No.1 Hospital, Wuhan, China

ARTICLE INFO

Article history:
Received 24 December 2021
Revised 24 February 2022
Accepted 13 March 2022

Keywords:
Linezolid-based chemotherapeutic regimens
postoperative multidrug-resistant spinal tuberculosis
efficacy
safety

ABSTRACT

Objectives: The study aimed to explore the efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.
Methods: The randomized controlled study included 50 *Mycobacterium tuberculosis* culture or pathological-confirmed multidrug resistant tuberculosis patients who received spinal surgery from January 2018 to February 2020. Twenty-five patients were assigned to the control group and the study group, respectively. Random number method was used for patient allocation and they were treated with levofloxacin, pyrazinamide, thioisonicotinamide enteric-coated tablet, amikacin sulfate injection, and sodium p-amino salicylate injection, accompanied by linezolid or not.
Results: The overall effective rate of the study group was higher than that of the control group (88.00% vs 64.00%, $P<0.05$). The severity of pain at 3 and 6 months postoperatively was lower in the study group than that in the control group ($P<0.05$). Postoperatively, the study group had higher bone graft fusion rate, shorter mean bone graft fusion time, and higher paraspinal cyst absorption rate than the control group ($P<0.05$). Postoperatively, the study group had lower levels of PCT, ESR, and CRP than the control group ($P<0.05$). All patients had normal hepatic and renal function, and no statistical difference of adverse effects between 2 groups were found.
Conclusions: Linezolid-based chemotherapeutic regimens can effectively treat patients with postoperative multidrug-resistant spinal tuberculosis but have higher rates of adverse reactions.

Introduction

Tuberculosis is listed as a significant respiratory tract disease in China and poses severe threat to the people's health. The World Health Organization (WHO) global tuberculosis survey found that in 2018, approximately 10 million patients died of tuberculosis worldwide. Currently, multidrug-resistant tuberculosis is a challenge in the field of tuberculosis treatment. Multidrug-resistant tuberculosis is defined as mycobacterium tuberculosis resistant to more than 1 antituberculosis drug, including rifampicin or isoniazide, at the same time (Lange et al., 2018). In Asia, joint tuberculosis, especially spinal tuberculosis, is a common secondary extrapulmonary tuberculosis, and drug-resistant spinal tuberculosis accounts for approximately 50% of joint tuberculosis cases (Guillouzouic et al., 2020). Nowadays, great attention has been paid clinically to the therapeutic regimens of postoperative multidrug-resistant tuberculosis, and 2 drug or multidrug regimens are recommended for the treatment of postoperative multidrug-resistant tuberculosis (Marfina et al., 2018, Vashakidze et al., 2021). Ethambutol is frequently used to treat pulmonary tuberculosis; it can inhibit *Mycobacterium tuberculosis* and other mycobacteria (Ghiraldi-Lopes et al., 2019). Prothionamide is a clinically commonly used antituberculosis drug and can inhibit the synthesis of mycolic acid in *Mycobacterium tuberculosis* (Hicks et al., 2019). Pyrazinamide

* Corresponding author: Ping Xia, Department of Orthopedics, The Central Hospital of Wuhan, No.26 Shengli Street, Jiangan District, Wuhan, Hubei 430014, China; Tel.: +86- 15607181066.
E-mail address: xiapingfm@163.com (P. Xia).
# Jie Qiao and Lin Yang contributed equally to this paper.

https://doi.org/10.1016/j.ijid.2022.03.020

may lower the oxygen utilization rate of *Mycobacterium tuberculosis*, thereby inhibiting metabolism in the mycobacterium and inducing death of mycobacteria (Tweed et al., 2019). However, because of the dense structure of the spinal bone tissues, bone tuberculous lesions are often surrounded by sclerotic bones and the lesions contain caseous material, pus, sequestra, and granulation, whereas the lung tissue is loose, and pulmonary tuberculous lesions mainly contain calcification, pus, caseous material, and granulation. Meanwhile, ethambutol, prothionamide, and pyrazinamide have lower permeability in spinal tuberculous lesions than pulmonary tuberculous lesions (Zou et al., 2014). Therefore, this study added linezolid, which is a kind of antibiotics and an inhibitor of protein synthesis in the bacteria. Linezolid has been widely used in the treatment of tuberculosis clinically (Shiraishi, 2014). Currently, there are very few clinical reports on the treatment of postoperative multidrug-resistant spinal tuberculosis with linezolid-based chemotherapeutic regimens.

This study aimed to explore the efficacy and safety of linezolid-based chemotherapeutic regimens for postoperative multidrug-resistant spinal tuberculosis patients.

Materials and methods

General data

There were 136 patients who received spinal surgery between January 2018 and February 2020 at Wuhan No. 1 Hospital and Wuhan Pulmonary Hospital. All patients were analyzed by *Mycobacterium tuberculosis* culture of surgical specimens or pathological examination for antituberculosis drug sensitivity test, including sensitivity to isoniazide, rifampicin, streptomycin, and ethambutol. A total of 41 patients were resistant to 1 drug, 45 patients were resistant to 2 or more drugs including isoniazide and rifampicin at the same time, and 50 patients were resistant to more than 1 drug including either isoniazide or rifampicin. These 50 patients with more than 1 drug-resistant patient were included into this prospective study. Twenty-five of them were assigned to the control group and the study group using the random number method. The age of the study group ranged from 22–65 years, with a mean age of (42.8±12.7) years. The duration of disease ranged from 5–61 (32.12±2.44) months. There were 13 (52.00%) males and 12 (48.00%) females. Clinical symptoms included fatigue in 13 (52.00%) cases, night sweats in 12 (48.00%) cases, low fever in 7 (28.00%) cases, poor appetite and reduced body weight in 15 (60.00%) cases, abscess in 15 (60.00%) cases, and regional pain in the diseased segments in 13 (52.00%) cases. The locations of lesions were the cervical spine in 1 (4.00%) case, the thoracic spine in 3 (12.00%) cases, the thoracolumbar spine in 7 (28.00%) cases, the lumbar spine in 9 (36.00%) cases, the lumbosacral spine in 4 (16.00%) cases, and the sacral spine in 1 (4.00%) case. The involved segments were single segments in 13 cases, double segments in 9 cases, and triple and more segments in 3 cases. Thoracolumbar kyphosis was present in 8 cases. The age of the control group was 22–64 years, with a mean age of (42.7±12.7) years. The duration of disease ranged from 6–60 (31.34±3.21) months. There were 14 (56.00%) males and 11 (44.00%) females. Clinical symptoms included fatigue in 12 (48.00%) cases, night sweats in 11 (44.00%) cases, low fever in 8 (32.00%) cases, poor appetite and reduced body weight in 14 (56.00%) cases, abscess in 14 (56.00%) cases, and regional pain in the diseased segments in 12 (48.00%) cases. The locations of lesions were the cervical spine in 1 (4.00%) case, the thoracic spine in 2 (8.00%) cases, the thoracolumbar spine in 10 (40.00%) cases, the lumbar spine in 8 (32.00%) cases, the lumbosacral spine in 3 (12.00%) cases, and the sacral spine in 1 (4.00%) case. The involved segments were single segments in 14 (56.00%) cases, double segments in 10 (40.00%) cases, and triple and above segments in 1 (4.00%) case. Thoracolumbar kyphosis was present in 7 (28.00%) cases. The 2 groups were comparable in general data ($P>0.05$) (Table 1). The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital. Informed consent was obtained from all patients included in this study.

Inclusion and exclusion criteria

Inclusion and exclusion criteria: (1) surgical indications included 1 of the following: (a) spinal stability or kyphosis, (b) spinal cord or nerve function impairment owing to compression, (c) relatively large abscess, cavity, sequestra, or sinus tract; (2) spinal tuberculosis was diagnosed by *Mycobacterium tuberculosis* culture or pathological examination; (3) first-time surgery for complete surgical debridement; (4) normal cardiac, hepatic, and renal function; (5) failure for 6 months of antituberculosis treatment excluding linezolid; (6) relatively good compliance and mentally normal; and (7) longer than 18 months follow-up time. The exclusion criteria were (1) concurrent active tuberculosis in other sites or other concurrent infectious disease; (2) concurrent rheumatoid arthritis, active rheumatoid arthritis, and other immune diseases; (3) refusal to participate in the study; (4) concomitant hematological disease; (5) long term use of corticoids; (6) allergy to the study drugs; (7) concurrent malignant tumors; (8) pregnant and lactating women; and (9) patients dead or loss to follow-up.

Methods

Surgical methods

Surgical debridement was performed on the basis of the pathophysiological changes of the spine in patients. Meanwhile, graft support and instrument internal fixation were implemented. Vertebral canal decompression was undertaken if neurological impairment was present. Surgical correction was done in patients with kyphosis. Surgical debridement of the lesions was the main surgical method in all patients. It was important to choose operation timing for the success of surgery (Xu, 2006), including: (1) standard and effective anti-tuberculosis chemotherapy for 3–4 weeks; (2) relief of systemic toxicity and improved general condition; (3) no fever, ESR<60 mm/h, and hemoglobin>100 g/L; and (IV) negative conversion of mycobacterium tuberculosis.

Chemotherapy regimens and side effect monitoring

Systemic therapy regimens including at least 4 drugs were given to patients according to drug sensitivity test before the operation for 4–6 weeks. The same regimens were continued to be implemented after the operation. Sputum, sequestrum, and granulation tissue obtained during surgery were sent for mycobacterium tuberculosis culture and sensitivity test again. The systemic therapy regimens were changed according to sensitivity test after the operation. Intensive treatment with 4 drugs were given for at least 6 months, and continuation treatment with 3 or more drugs were given for 6–18 months (Qin et al., 2009).

Blood routine examination, liver function, renal function, and erythrocyte sedimentation rate (ESR) were tested every month. Side effects of systemic therapy regimens, which included dermatitis, hepatic dysfunction, myelosuppression, leukopenia, and gastrointestinal reaction, were monitored.

Postoperative treatment

The control group were given levofloxacin, pyrazinamide, thioisonicotinamide enteric-coated tablet, amikacin sulfate injection, and sodium p-amino salicylate injection. Levofloxacin (registered number of approval: SFDA Approval No. H20000655; Manufacturer: Daiichi Sankyo Co. [Beijing] Limited) was taken orally at

Table 1
Baseline characteristics of included patients

Variables	Study (%)	Control (%)	*P*-value
Age	42.8±12.7	42.7±12.7	0.978
Sex (male/female)	13/12	14/11	0.777
Duration of disease	32.12±2.44	31.34±3.21	0.336
Symptoms			1.000
Fatigue	13 (52.00%)	12(48.00%)	
Night sweats	12 (48.00%)	11 (44.00%)	
Low fever	7 (28.00%)	8 (32.00%)	
Poor appetite and reduced body weight	15 (60.00%)	14 (56.00%)	
Abscess	15 (60.00%)	14 (56.00%)	
Regional pain	13 (52.00%)	12 (48.00%)	
Location			0.968
Cervical	1 (4.00%)	1 (4.00%)	
Thoracic	3 (12.00%)	2 (8.00%)	
Thoracolumbar	7 (28.00%)	10 (40.00%)	
Lumbar	9 (36.00%)	8 (32.00%)	
Lumbosacral	4 (16.00%)	3 (12.00%)	
Sacra	1 (2.00%)	1 (2.00%)	
Number of involved segment			0.579
1	13 (52.00%)	14 (56.00%)	
2	9 (36.00%)	10 (40.00%)	
3 or more	3 (12.00%)	1 (4.00%)	
Thoracolumbar kyphosis	8 (32.00%)	7 (28.00%)	0.907
Complication			
Hypertension	2 (8.00%)	3 (12.00%)	0.637
Diabetes	1 (4.00%)	2 (8.00%)	0.552
History of chemotherapy			0.934
No treatment	20 (80.00%)	19 (76.00%)	
Once for extra-pulmonary tuberculosis	4 (16.00%)	5 (20.00%)	
Twice for extra-pulmonary tuberculosis	1 (4.00%)	1 (4.00%)	
Time from diagnosis to surgery (week)	8.51±1.43	8.43±1.01	0.821

0.1 g, 3 times daily; pyrazinamide (registered number of approval: SFDA Approval No. H51020876; manufacturer: Chengdu Jinhua Pharmaceutical Co. Limited) was taken at a draught 15–30 mg/kg per day (2 g maximum per day). Oral thioisonicotinamide enteric-coated tablet (approval no. 44020704; manufacturer: Guangdong South China Pharmaceutical Group Co., LTD.), 250 ml/time, 3 times/d; Amikacin sulfate injection (approval No. H51020724; manufacturer: Chengdu Tiantaishan Pharmaceutical Co., LTD.), intravenous infusion, the first dose by weight 10 mg/kg, followed by 7.5 mg/kg every 12 hours or 15 mg/kg every 24 hours; sodium p-amino salicylate (approval No. H23021719; manufacturer: Harma Pharmaceutical Group Pharmaceutical General Factory), intravenous infusion, 10 g/time per day, before use, added with an appropriate amount of sterilized water for injection, diluted with 500 ml 5% glucose injection, and dropped for 2–3 h.

On top of the previously mentioned drugs, the study group received linezolid (registered number of approval: SFDA approval No. H20090516; manufacturer: Pfizer Pharmaceuticals LLC). Linezolid was initially infused at a dose of 600 mg twice daily and after 1–2 months (the intensification phase), the dose was modified to 600 mg once daily, on the basis of the tolerability of the patients and adverse reactions or changed to oral linezolid at a dose of 600 mg once daily. Treatment regimens lasted for 6 months in both groups (Qin et al., 2009).

Observational parameters

Pain, laboratory parameters, and radiological changes in the 2 groups were observed, and efficacy and safety were analyzed.

Clinical efficacy: According to "Chemotherapeutic Guidelines for Drug-resistant Tuberculosis (2015)" (China Antituberculosis Society) and the treatment characteristics of multidrug-resistant joint tuberculosis, the clinical efficacy for multidrug-resistant spinal tuberculosis was evaluated as follows: (1) cured: no recurrence 1 year after discontinuation of treatment upon completion of scheduled treatment; (2) effective: treatment was discontinued for less than 1 year and no recurrence during follow-up after completion of scheduled treatment; (3) ineffective: no cure was achieved or scheduled treatment was not completed. Overall effective rate = (cure + effective) patient/all patients.

Pain: Pain was evaluated before surgery and 3 and 6 months after the operation using the Visual Analog scale (VAS) (Winebrake et al., 2020). The score ranges between 0 and 10, with higher scores indicating more severe pain.

Laboratory evaluation: 5 to 8 ml venous blood was obtained from patients before and after treatment and was stored at –50°C after centrifugation until further use. After centrifugation, procalcitonin (PCT) was determined by electrochemiluminescent method using kits from Shanghai Toujing Life Science Co. Ltd. Erythrocyte sedimentation rate (ESR) was determined using Monitor-100 (Vital) and related products and C reactive protein (CRP) was measured using automatic biochemical analyzer by enhanced immune turbidometry. The kits were purchased from Shanghai OPM Biosciences Co. Ltd and used in strict accordance with the manufacturer's instructions.

Radiological changes: (1) Postoperative bone graft fusion rate and bone graft fusion time were observed and the criteria for bone graft fusion followed the literature. (2) Preoperative and postoperative MRI changes around paraspinal abscess in the 2 groups were observed.

Safety: Blurred vision, tinnitus, hearing impairment, perioral numbness, gastrointestinal reactions (vomiting, nausea), fever, peripheral neuritis, and rash were recorded in detail. Meanwhile, cardiac, hepatic, and renal function tests were undertaken.

Statistical methods

Data were analyzed using SPSS 21.0 statistical software. Normally distributed measurement data were expressed as mean±standard deviation (SD), and the comparisons were examined by Student *t* test. The categorical data were expressed as n(%), and the differences between the 2 groups were examined by chi-

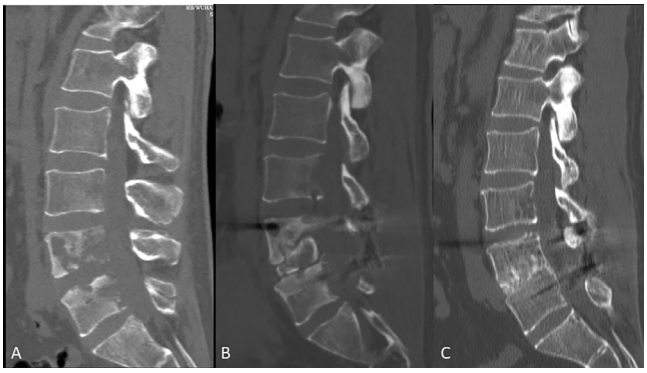

Figure 1. Spinal tuberculosis before and after surgery. A: before surgery; B: 3 months after surgery, focal infection without healing; C: 12 months after surgery, recovery.

square analysis or Fisher exact test. Ranked data were examined by rank-sum test. A *P*-value below 0.05 was considered significant.

Results

In the study, 50 patients with postoperative multidrug-resistant spinal tuberculosis received 6 months of continuous therapy and completed follow-up visits. The overall effective rate of the study group was significantly higher than that of the control group (88.00% vs 64.00%, P=0.017).

There was no statistical difference in pain severity between the 2 groups before surgery (P=0.956); whereas, the pain of patients in the study group was significantly lower than that of control group (P<0.001).

Patients in the study group had a significantly higher bone graft fusion rate (P=0.017), shorter mean bone graft fusion time (P=0.004), and greater paraspinal cyst absorption rate (P=0.021) than the patients in the control group after surgery (Figure 1).

There was no statistical difference in the preoperative levels of PCT (P=0.726), ESR (P=0.910), and CRP (P=0.967) between the 2 groups.

The study group had significantly lower levels of PCT (P=0.013), ESR (P=0.009), and CRP (P=0.036) than the control group after surgery.

There was no statistical difference in the incidence of adverse effects between the groups (P=0.395). All patients had normal hepatic and renal function.

All results mentioned above are displayed in Table 2.

Table 2
Comparison of indexes between two groups

Variables	Study	Control	*P*-value
Effective rate	23 (88.00%)	16 (64.00%)	0.017
Cure	13	9	
Effective	9	8	
Ineffective	3	8	
Pain at different time			
Before surgery	6.03±1.29	6.01±1.25	0.956
3 months after surgery	2.61±0.22	2.98±0.28	<0.001
6 months after surgery	2.01±0.14	2.35±0.17	<0.001
Radiological parameters			
Bone graft fusion rate	23 (92.00%)	16 (64.00%)	0.017
Mean bone graft fusion time	8.09±1.08	9.13±1.32	0.004
Paraspinal cyst absorption rate	24 (96.00%)	18 (72.00%)	0.021
Laboratory parameters*			
PCT (μg/L)	3.12±0.21	3.10±0.19	0.726
ESR (mm/h)	93.92±7.82	93.67±7.79	0.910
CRP (mg/L)	60.87±6.83	60.79±6.79	0.967
Laboratory parameters#			
PCT (μg/L)	0.49±0.07	0.53±0.03	0.013
ESR (mm/h)	27.23±2.39	28.96±2.13	0.009
CRP (mg/L)	22.02±3.01	23.89±3.11	0.036
Safety	15 (60.00%)	12 (48.00%)	0.395
Peripheral neuritis	4	1	
albuminuria	1	0	
Hypertension	0	1	
Hypoglycemia	0	1	
Thrombocytopenia	1	1	
Myelosuppression	0	0	
Anemia	3	2	
Dizziness	1	2	
Gastrointestinal Reaction	3	3	
Rash	2	1	

* preoperative parameters
# postoperative parameters.

Discussion

Spinal tuberculosis is a common secondary extrapulmonary tuberculosis in clinical practice, and in the absence of prompt and effective treatment, spinal tuberculosis may lead to abscess, spinal function impairment, loss of spinal stability, kyphosis, and even hemiplegia because of compression of the spinal cord and nerves (Khanna and Sabharwal, 2019). Currently, supportive therapy, surgical treatment, and pharmacotherapy are used to treat multidrug-resistant bone tuberculosis. Among them, pharmacotherapy is most commonly used clinically. Pharmacotherapy of multidrug-resistant spinal tuberculosis is mainly based on the results of drug sensitivity test of *Mycobacterium tuberculosis*, history of drug use, tolerance by patients of antituberculosis drugs, and the WHO treatment guidelines for drug resistant tuberculosis; treatment plans are made according to the specific conditions of the patients (Binefa et al., 2014). The purpose of surgical treatment of multidrug-resistant spinal tuberculosis is complete removal of lesions, relief of spinal cord and nerve compression, correction of kyphosis, and construction of spinal stability (Dreyer, 2005). In addition, because *Mycobacterium tuberculosis* grows under the long-term selection pressure of antituberculosis drugs, drug resistance gradually emerges, lowering the effectiveness of treatment for multidrug-resistant spinal tuberculosis. Therefore, this study explored the efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.

Linezolid is a first generation oxazolidinone antibiotic and exerts its action by inhibiting protein synthesis in the bacteria. Linezolid selectively acts on 50S ribosomal subunit to inhibit the coupling between mRNA and ribosome and prevents the formation of 70S initiation complex, thereby inhibiting bacterial protein synthesis in the early phase of translation. Because of its unique action sites, linezolid does not have cross-drug resistance with commonly used antituberculosis drugs and also does not readily induce *Mycobacterium tuberculosis* drug resistance in vitro (Han and Yim, 2019). Therefore, in 2016 and 2018, the WHO guidelines on drug-resistant tuberculosis lists linezolid as a core medication for the treatment of multidrug-resistant tuberculosis. Previous studies showed the content of linezolid in the bone tissues was 40.1%–60.0% of the plasma content in rheumatoid arthritis and degenerative joint diseases (Li et al., 2020, Lovering et al., 2002, Schwameis et al., 2017) but was still with high penetrability into bone tissue after 24-h oral administration (Li et al., 2019). In the past, linezolid was frequently used to treat multidrug-resistant pulmonary tuberculosis, but there are few studies on the clinical efficacy of linezolid for multidrug-resistant spinal pulmonary tuberculosis. The current results revealed that the study group had a higher overall effectiveness rate than the control group (P<0.05), suggesting that linezolid-based chemotherapeutic regimens can effectively treat patients with postoperative multidrug-resistant spinal tuberculosis. This is because linezolid has a more potent

anti-*Mycobacterium tuberculosis* activity, its minimal inhibitory concentration (MIC) for *Mycobacterium tuberculosis* is 0.125–1 mg/L, and linezolid has antibacterial activities for both drug-sensitive and resistant strains, and it can act against logarithmically growing and resting colonies. Agyeman et al showed that linezolid had a MIC of 0.125–4 mg/L for *Mycobacterium tuberculosis* (Agyeman and Ofori-Asenso, 2016), and its success rate and the rate of negative conversion in the sputum were apparently better than regimens without linezolid. Meanwhile, linezolid has a low inhibitory concentration for multidrug-resistant *Mycobacterium tuberculosis*, and its plasma concentration is relatively higher; multidrug-resistant *Mycobacterium tuberculosis* has a relatively low rate of resistance against linezolid. *Mycobacterium tuberculosis* has a relatively low rate of exposure to linezolid, and linezolid may have synergy with other drugs in the regimen. In addition, 4 patients with postoperative multidrug-resistant spinal tuberculosis in this study failed the linezolid-based chemotherapeutic regimens likely because of the emergence of linezolid resistance at the start of or during treatment of *Mycobacterium tuberculosis*. Because the study did not carry out sequencing analysis of linezolid resistant genes in *Mycobacterium tuberculosis*, further studies are required. In addition, comprehensive drug-sensitivity testing of *Mycobacterium tuberculosis* should be done in the 4 patients who failed treatment and new effective antituberculosis protocol should be established on the basis of the results of the drug-sensitivity tests.

For the systemic regimens and time duration, WHO recommended 9–11 months treatment enrolling bedaquiline as 1 of regimens for patients with multidrug-resistant tuberculosis, making the regimen all oral. For patients with fluoroquinolone resistance, WHO recommended regimens composed of bedaquiline, pretomanid, and linezolid under operational research conditions for 6–9 months (Mirzayev et al., 2021). Besides, patients with more extensive tuberculosis and severe disease should receive 18–20 months of treatment on the basis of individual conditions. The enrollment of bedaquiline had previously shown its effectiveness and safety in a Chinese population (Han et al., 2020). Although not exactly the same, ATS/CDC/ERS/IDSA Clinical Practice Guideline recommended that patients with multidrug-resistant tuberculosis receive intensive treatment for 5–7 months and continuation treatment for 15–21 months but with low evidence level. Besides, longer treatment duration would induce more toxicity and costs for patients (Nahid et al., 2019).

Up to now, there was still no recommendation for postoperative systemic regimens and duration for multidrug-resistant tuberculosis and it should be discussed in the future. In this study, 6-month regimens, including linezolid, resulted in favorable outcomes, which might be a potential choice and issue for further studies (Nahid et al., 2019).

Postoperative pain is a complex physiological and psychological response to tissue injury and repair in humans and is an issue each patient has to tackle postoperatively. Postoperative pain causes psychosomatic suffering to patients, is a major cause of postoperative complications, and greatly impacts the postoperative quality of rehabilitation and life of the patients (Mirelman et al., 2019). Therefore, postoperative pain has become 1 of the important clinical indicators. The current results showed that pain at 3 and 6 months after the operation was less severe in the study group than in the control group ($P<0.05$), suggesting that linezolid-based chemotherapeutic regimens can effectively relieve postoperative pain in patients with multidrug-resistant spinal tuberculosis.

Spinal fusion refers to postoperative bony fusion of 2 or more vertebral segments via bone graft and is a guarantee of long-term spinal stability. Only firm bony fusion can achieve 3 column stabilization and promote rehabilitation of patients (Baudendistel et al., 2019). Therefore, spinal fusion rate is an important indicator of postoperative spinal condition. The current results showed that postoperatively, the study group had a higher bone graft fusion rate, shorter mean bone graft fusion time, and a lower paraspinal cyst absorption rate than the control group ($P<0.05$), suggesting that linezolid-based chemotherapeutic regimens can effectively increase the bone graft fusion rate and paraspinal cyst absorption rate and reduce the mean bone graft fusion time in patients with postoperative multidrug-resistant spinal tuberculosis. This is likely owing to increased spinal stability in postoperative patients undergoing graft fusion and effective control of inflammation in tuberculous lesions, thereby effectively alleviating pain.

PCT, ESR, and CRP are plasma biomarkers currently used for monitoring tuberculosis and infection. Among them, ESR belongs to acute phase protein and is often used for evaluation of development and recovery of inflammation, and it is an important indicator of disease severity. PCT is a precursor of calcitonin and is at low levels in the normal state. When inflammation occurs upon infection, plasma PCT increases. PCT is an important parameter for evaluating cellular infectious diseases. CRP is an acute-phase protein and effectively evaluates the severity of inflammation. Yang et al showed that ESR, CRP, and PCT may be used as inflammation markers for early diagnosis of spinal tuberculosis (Baudendistel et al., 2019). The current results showed that the study group had lower postoperative plasma levels of PCT, ESR, and CRP than the control group ($P<0.05$), suggesting that linezolid-based chemotherapeutic regimens can effectively lower postoperative PCT, ESR, and CRP levels in patients with multidrug-resistant spinal tuberculosis, lower the levels of inflammatory factors, and prevent infection.

The safety of linezolid for multidrug-resistant tuberculosis is a clinical issue worthy of attention. The rate of linezolid discontinuation owing to severe adverse reactions was 15.81%. The incidence of gastrointestinal tract adverse reactions is 33.60%. The incidence of peripheral neuritis is 29.92%, and the development of peripheral neuritis does not have apparent correlation with the dose of linezolid (Tuberculosis Branch of Chinese Medical Association, 2018). The current results showed that there was no statistical difference in the incidence of adverse reactions between the 2 groups ($P>0.05$), and all patients had normal hepatic and renal function, suggesting that linezolid-based chemotherapeutic regimens are associated with a relatively high rate of adverse reactions in the treatment of patients with postoperative multidrug-resistant spinal tuberculosis. In this study, peripheral neuritis manifested as mild numbness of the 4 limbs, and vitamin B was given to these patients. Patients with anemia and thrombocytopenia were mild and without symptoms, for whom blood transfusion treatment and reduced linezolid were given. All patients recovered after 2 weeks of blood transfusion. Expectant treatment was given to patients with albuminuria. Dizziness was lessened after the dose of linezolid was reduced. Gastrointestinal reaction manifested as nausea, vomiting, and abdominal distension and improved after treatment with gastrointestinal motility drugs. Patients with rash had rash in axilla, which was eczema, 2 cm in diameter, and was diagnosed as eczema by dermatologists, and improved by external medication.

There were also several limitations in this study. First, this was a small sample size study in single center because of the scarcity of surgery on spinal tuberculosis. Second, there was still no consensus on postoperative regimens and duration of linezolid. Third, a relatively high rate of adverse effects limited the application of linezolid in clinical practice. Thus, all results in this study should be interpreted cautiously.

Overall, linezolid-based chemotherapeutic regimens would increase the clinical efficacy; reduce pain; enhance bone graft fusion rate and paraspinal cyst absorption rate; shorten mean bone graft fusion time; reduce PCT, ESR, and CRP levels; and lower the levels of inflammatory factors in patients with postoperative multidrug-resistant spinal tuberculosis.

Data Availability

All relevant data are within the paper.

Funding

The Research Project of Wuhan Municipal Health Commission (No.WX21M02).

Contributions

Jie Qiao and Chang Cheng designed the study, analyzed the data, and wrote the manuscript. Jing Feng, Xiyong Dai, Feng Xu, and Ping Xia participated in the data collection, analysis, and interpretation. Ping Xia was supervised the study. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no competing interests to declare.

References

Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob 2016;15(1):41.

Baudendistel ST, Schmitt AC, Rodriguez AV, McFarland NR, Hass CJ. A turn for the worse: Turning performance in Parkinson's disease and Essential tremor. Clin Biomech (Bristol, Avon) 2019;70:245–8.

Binefa G, Rodríguez-Moranta F, Teule A, Medina-Hayas M. Colorectal cancer: from prevention to personalized medicine. World J Gastroenterol 2014;20(22):6786–808.

Dreyer G. Operative management of cervical cancer. Best Pract Res Clin Obstet Gynaecol 2005;19(4):563–76.

Ghiraldi-Lopes LD, Campanerut-Sá PAZ, Evaristo GPC, Meneguello JE, Fiorini A, Baldin VP, et al. New insights on Ethambutol Targets in Mycobacterium tuberculosis. Infect Disord Drug Targets 2019;19(1):73–80.

Guillouzouic A, Andrejak C, Peuchant O, Hery-Arnaud G, Hamdad F, Lanotte P, et al. Treatment of Bone and Joint Tuberculosis in France: A Multicentre Retrospective Study. J Clin Med 2020;9(8).

Han J, Yim JJ. Linezolid for drug-susceptible tuberculosis. Lancet Infect Dis 2019;19(5):468–9.

Han X, Chen X, Sha W, Zhang X, Qiu L, Wang J, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis in China. Int J Tuberc Lung Dis 2020;24(8):789–94.

Hicks ND, Carey AF, Yang J, Zhao Y, Fortune SM. Bacterial Genome-Wide Association Identifies Novel Factors That Contribute to Ethionamide and Prothionamide Susceptibility in Mycobacterium tuberculosis. mBio 2019;10(2).

Khanna K, Sabharwal S. Spinal tuberculosis: a comprehensive review for the modern spine surgeon. Spine J 2019;19(11):1858–70.

Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K. Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment. Respirology 2018;23(7):656–73.

Li Y, Dong W, Lan T, Fan J, Qin S, Guo A. Distribution of Linezolid in Tuberculosis Lesions in Patients with Spinal Multidrug-Resistant Tuberculosis. Antimicrob Agents Chemother 2020;64(7).

Li Y, Huang H, Dong W, Lan T, Fan J, Wen S, et al. Penetration of linezolid into bone tissue 24 h after administration in patients with multidrug-resistant spinal tuberculosis. PLoS One 2019;14(10).

Lovering AM, Zhang J, Bannister GC, Lankester BJ, Brown JH, Narendra G, et al. Penetration of linezolid into bone, fat, muscle and haematoma of patients undergoing routine hip replacement. J Antimicrob Chemother 2002;50(1):73–7.

Marfina GY, Vladimirov KB, Avetisian AO, Starshinova AA, Kudriashov GG, Sokolovich EG, et al. Bilateral cavitary multidrug- or extensively drug-resistant tuberculosis: role of surgery. Eur J Cardiothorac Surg 2018;53(3):618–24.

Mirelman A, Bonato P, Camicioli R, Ellis TD, Giladi N, Hamilton JL, et al. Gait impairments in Parkinson's disease. Lancet Neurol 2019;18(7):697–708.

Mirzayev F, Viney K, Linh NN, Gonzalez-Angulo L, Gegia M, Jaramillo E, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J 2021;57(6).

Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med 2019;200(10):e93–e142.

Qin SB, Dong WJ, Xu SZ. Retrospective analysis of systemic therapy for spinal tuberculosis. Journal of Third Military Medical University 2009;31(20):1929–31.

Schwameis R, Syré S, Sarahrudi K, Appelt A, Marhofer D, Burau D, et al. Penetration of linezolid into synovial fluid and muscle tissue after elective arthroscopy. J Antimicrob Chemother 2017;72(10):2817–22.

Shiraishi Y. Surgical treatment of nontuberculous mycobacterial lung disease. Gen Thorac Cardiovasc Surg 2014;62(8):475–80.

Tweed CD, Dawson R, Burger DA, Conradie A, Crook AM, Mendel CM, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med 2019;7(12):1048–58.

Tuberculosis Branch of Chinese Medical Association. Expert consensus report of Linezolid on anti-tuberculosis. Chin J of Tuberc Respir Dis 2018;41(01):14–19.

Vashakidze SA, Gogishvili SG, Nikolaishvili KG, Avaliani ZR, Chandrakumaran A, Gogishvili GS, et al. Adjunctive surgery versus medical treatment among patients with cavitary multidrug-resistant tuberculosis. Eur J Cardiothorac Surg 2021;60(6):1279–85.

Winebrake JP, Lovecchio F, Steinhaus M, Farmer J, Sama A. Wide Variability in Patient-Reported Outcomes Measures After Fusion for Lumbar Spinal Stenosis: A Systematic Review. Global Spine J 2020;10(2):209–15.

Xu JZ. Rerecognition of surgical indications and methods for spinal tuberculosis. Chinese Journal of Spinal cord 2006(12):889–90.

Zou MX, Li J, Lv GH, Wang B, Deng YW. Treatment of thoracic or lumbar spinal tuberculosis complicated by resultant listhesis at the involved segment. Clin Neurol Neurosurg 2014;125:1–8.