SPANDIDOS PUBLICATIONS

EXPERIMENTAL AND THERAPEUTIC MEDICINE 11: 777-782, 2016

Efficacy and effect of free treatment on multidrug-resistant tuberculosis

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Received September 2, 2015; Accepted December 29, 2015

DOI: 10.3892/etm.2015.2966

Abstract. Multidrug-resistant tuberculosis (MDR-TB) is a serious public health and social issue. It pertains to the type of tuberculosis that is resistant simultaneously to isoniazid and rifampicin. MDR-TB has a high mortality and is expensive to treat. The aim of the present study was to examine the therapeutic effects of individualized free treatment and the relevant influencing factors on the treatment outcome for MDR-TB. A prospective study module was used to analyze the therapeutic outcome of MDR-TB with individualized free treatment for 160 patients between 2011 and 2014. Statistical analysis was performed using the Chi-square or Fisher's exact test, and the odds ratio was calculated using a logistic regression analysis model. In total, 160 patients were enrolled in the study for treatment of MDR-TB. From these, 88 cases completed the course of treatment, and 70 cases were successfully treated. Of the remaining 72 cases, 37 cases exhibited treatment failure, 18 cases were suspended during treatment and 17 patients succumbed to the disease. The results showed that the confounding factors were: i) retreatment ($p<0.05$); ii) occurrence of diabetes ($p<0.001$); iii) lesion without improvement in radiography during treatment ($p=0.001$); iv) positive sputum culture for Mycobacterium tuberculosis after 3-month treatment ($p<0.05$); and v) termination of treatment due to adverse reaction ($p<0.05$). These factors were associated with poor treatment outcomes by logistic regression analysis. Adverse drug reaction was observed in 33 cases and treatment was terminated or changed permanently in 29 of these cases. The most common adverse reaction was liver function damage caused by pyrazinamide and leucopenia caused by rifabutin. One patient suffered from serious liver failure. In conclusion, the success rate of long treatment course for MDR-TB is not high due to many adverse reactions. Occurrence of diabetes is the main factor that caused poor efficacy.

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Key words: multidrug-resistant tuberculosis, individualized treatment, efficacy, adverse reactions

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a serious public health and social issue that has gained global attention. It refers to the type of tuberculosis that is resistant to isoniazid and rifampicin at the same time (1). Extensively drug-resistant TB (XDR-TB) is a form of TB caused by organisms that are resistant to isoniazid and rifampicin, i.e., MDR-TB, as well as any fluoroquinolone or second-line anti-TB injectable drugs such as amikacin, kanamycin or capreomycin (1). MDR-TB is expensive to treat, has a low treatment success rate and high mortality. The World Health Organization (WHO) reported that there were ~450,000 cases of MDR-TB in 2012, and the majority of these cases occurred in China, India and Russia (1). Therefore, treatment of patients with MDR-TB is crucial in regulating tuberculosis, albeit the disease continues to pose a challenge. Containment of MDR-TB in Shanghai has resulted in the launch of a new policy of free treatment for patients with MDR-TB in November, 2011.

An established Shanghai expert group on MDR-TB, following diagnosis and confirmation thereof, administered individualized treatment to MDR-TB patients (2). It was explicitly stipulated that patients with MDR-TB whose household registration was in the region of Shanghai or who had a temporary residential permit of Shanghai were exempted from hospitalization costs. Free medical supplies and tests included antituberculosis drug therapy over a period of 2 years, sputum smear test for acid-fast bacillus each month, mycobacterial culture, mycobacterial strain subspecies identification, drug sensitivity test and chest X-ray/computed tomography (CT), blood and urine test and blood biochemical examinations.

The aim of this study was to examine the efficacy of free and individualized treatment administered over a period of 4 years to patients with MDR-TB and determine its associated influencing factors, to provide objective reference for policy makers.

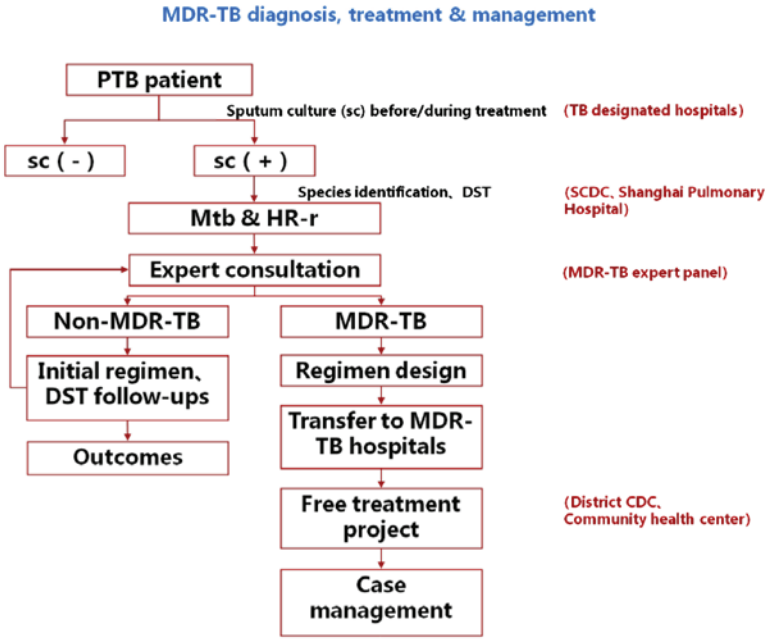

Figure 1. Flow chart of diagnosis and treatment. MDR-TB, multidrug-resistant tuberculosis; DST, drug susceptibility testing.

Materials and methods

Ethics approval. This study was approved by the Shanghai Pulmonary Hospital Medical Ethics Committee (Shanghai, China) and the patients signed informed consent prior to participating in the study.

Inclusion criteria. The inclusion criteria for the study were: i) Patients whose household registration was Shanghai or who had a temporary residential permit of Shanghai; ii) patients who were able to provide a test report of positive sputum mycobacterium culture and drug susceptibility testing within the previous 2 months and were confirmed cases of MDR-TB; and iii) the features of radiography were consistent with the manifestation of the pulmonary tuberculosis.

Diagnosis and treatment procedures. An MDR-TB expert group situated in Shanghai held monthly seminars on MDR-TB, for the diagnosis of patients with MDR-TB and establishment of individualized treatment plans for the various types of tuberculosis. Additionally, the expenses of patients in this area were covered and free medication was dispensed for diagnosis and treatment. At the same time, under the guidance of district (county) center for disease control and prevention, the community health service center supervised and managed patients with MDR-TB within their district during non-hospitalization, by focusing close attention on the adverse reactions of patients once these were identified, and urging patients to undergo hospitalization (Fig. 1).

Principle of treatment. The MDR-TB expert group created an individualized treatment regimen based on the results of the drug sensitivity test and medication history of anti-tuberculosis drugs. According to WHO five group classification of anti-TB drugs (3), a treatment scheme should at least include four anti-TB drugs that are considered effective or possibly effective, over a total treatment period of 18-24 months and ≥6-month injections.

Observation indices. Selected patients were inspected for acid-fast bacilli in sputum smears and Mycobacterium culture (positive bacteria identification and drug sensitivity tests). Blood, urine test and blood biochemistry (liver and kidney function/uric acid) tests were carried out monthly, with records of clinical symptoms and adverse reactions, and chest radiograph/CT every 2 months until the end of treatment.

Treatment outcome. Treatment outcome was classified as cured, completed treatment, defaulted, died, or failed as per the WHO guidelines (4). Criteria for each treatment outcome were: i) cure: patients completed treatment without any evidence of failure, with ≥3 consecutive negative sputum culture ≥30 days apart following the intensive phase. ii) Completed treatment: patients completed treatment without any evidence of failure, but without evidence of ≥3 consecutive negative sputum culture ≥30 days apart following the intensive phase. iii) Fail: patients had to terminate treatment or change treatment plan (change with >2 drugs) permanently owing to sputum culture not turning to negative at the end of the intensive phase or following sputum culture turning to negative, it became positive again; the mycobacterium tuberculosis resisted fluoroquinolones and injectables and adverse drug reactions. iv) Death: patients succumbing due to any reason during treatment. v) Lost to follow up: patients were not treated or treatment interrupted for any reasons for >2 consecutive months. vi) Treatment success: included cure and completing treatment.

Bacteriology was considered negative when two consecutive sputum cultures were identified to be negative ≥30 days apart. In addition, if bacteriology initially identified as negative turned to positive, then two consecutive positive sputum cultures ≥30 days apart were identified as positive.

Table I. Drug resistant profile of 160 cases.

Drug resistant profile	Cases (%)
SHRE[a]	83 (51.9)
SHR	47 (29.4)
HRE	8 (5.0)
HR	22 (13.8)

[a]S, streptomycin; H, isoniazid; R, rifampicin; E, ethambutol.

Statistical analysis. Data analysis was performed using SPSS software (SPSS, Inc., Chicago, IL, USA). A comparison of rates between the groups was carried out using the Chi-square or Fisher's exact test to get meaningful factors. The odds ratio (OR) and the 95% confidence interval (CI) were calculated using the forward method entered using the logistic regression analysis model to obtain the influencing factors of therapy outcome. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General. Between April 2011 and October 2014, 160 patients with confirmed MDR-TB and completed anti-TB treatment, and human immunodeficiency virus negative were enrolled in this study. Of the 160 patients, 119 were males and 41 were females, with an average age of 47.4±10.4 years. There were 35 cases of newly diagnosed MDR-TB and 125 cases of retreatment with MDR-TB. Of the 125 cases, 83 cases exhibited drug resistance to four of the first-line drugs, including streptomycin, isoniazid, rifampicin and ethambutol. In 55 cases there was drug resistance to three first-line drugs (isoniazid; rifampicin, ethambutol or streptomycin; isoniazid and rifampicin), and 22 cases were resistant to two first-line drugs, including isoniazid and rifampicin (Table I).

Treatment outcome and its influencing factors. A total of 160 patients completed the treatment of MDR-TB, with 58 cases becoming sputum negative after a three-month treatment (36.3%). At the end of the course of treatment, 88 cases had been successfully treated (55.0%), with 70 cases being cured (43.8%), while 18 cases completed treatment but were not cured (11.3%). There were 37 failed cases (23.1%), 18 suspended cases during treatment (11.3%), and 17 cases of mortality (10.6%). We analyzed the factors associated with treatment outcome of MDR-TB, including gender, age, initial treatment/retreatment, combined diabetes, scopes of radiography lesion, change of radiography lesion during treatment, and termination of treatment or permanent replacement of treatment caused by adverse reactions.

Using the Chi-square or Fisher's exact test, the p-values obtained were: initial treatment/retreatment (p=0.030), XDR-TB (p=0.028), sputum culture became negative after 3-month treatment (p=0.000), change of radiography during treatment (p=0.001), whether complicated by diabetes or not (p=0.000), and termination of treatment or permanent replacement of treatment caused by adverse reactions (p=0.001).

Table II. Treatment outcome and its influencing factors (n=160).

Factors	Successful 88 cases (%)	Unsuccessful 72 cases (%)	P-value
Gender			0.142
Male	62 (70.5)	58 (80.6)	
Female	26 (29.5)	14 (19.4)	
≥60 years			0.220
Yes	11 (12.5)	14 (19.4)	
No	77 (87.5)	58 (80.6)	
Initial treatment			0.030
Yes	27 (30.7)	8 (11.1)	
No	61 (69.3)	64 (88.9)	
XDR-TB			0.028
Yes	4	11	
No	84	61	
Combined diabetes			0.000
Yes	8 (9.1)	27 (37.5)	
No	80 (90.9)	45 (62.5)	
Scopes of lesion ≥3 lung fields			0.600
Yes	42 (47.7)	48 (66.7)	
No	26 (29.5)	14 (19.4)	
Radiography lesion with improvement			0.000
Yes	65 (73.9)	28 (38.9)	
No	23 (26.1)	44 (61.1)	
Sputum culture conversion after 3-month treatment			0.000
Yes	45 (51.1)	13 (18.1)	
No	43 (48.9)	59 (81.9)	
Permanent replacement of treatment caused by adverse reactions or termination of treatment			0.001
Yes	8 (9.1)	21 (29.2)	
No	80 (90.9)	51 (70.8)	

XDR-TB, extensively drug-resistant tuberculosis.

Other comparisons included effect of gender (p=0.142); age of ≥60 years old or not (p=0.220), and scopes of lesion ≥3 lung fields or not (p=0.600) were not associated with treatment outcome (Table II). The logistic regression method was used for subsequent multiple-factor analysis. The results showed that some independent risk factors associated with poor treatment outcome were as follows: i) retreatment (OR=4.393, 95% CI: 1.551-12.444, p=0.005), ii) combined diabetes (OR=6.460, 95% CI: 2.276-18.336, p=0.000), iii) radiography lesion without any improvement (OR=4.130, 95% CI: 1.729-9.865, p=0.001), iv) positive sputum culture for 3-month treatment

Table III. Logistic regression method for multiple-factor analysis.

Factors	β-value	OR (95% CI)	P-value
Retreatment	1.480	4.393 (1.551-12.444)	0.005
Combined diabetes	1.866	6.460 (2.276-18.336)	0.000
Radiography lesion without any improvement	1.418	4.130 (1.729-9.865)	0.001
Positive sputum culture for 3-month treatment	1.110	3.033 (1.243-7.403)	0.015
Termination of treatment or permanent replacement of treatment caused by adverse reactions	1.373	3.946 (1.355-11.495)	0.012

OR, odds ratio; CI, confidence interval.

(OR=3.033, 95% CI: 1.243-7.403, p=0.015) and v) termination of treatment or permanent replacement of treatment caused by adverse reactions (OR=3.946, 95% CI: 1.355-11.495, p=0.012) (Table III).

Safety evaluation. Adverse drug reaction was identified 46 times in 33 patients (25.4%), and 43 times were required to arrest the related anti-TB drugs. The most common adverse reaction was liver function damage (26 times) to drugs including p-aminosalicylic acid injection, protionamide tablets, pyrazinamide tablets. The second most common adverse reaction was leucopenia (7 times) caused by rifabutin capsules. Other adverse reactions included kidney damage, joint pain, rash and mental disorders (Table IV), with 1 time of severe adverse reactions of liver failure, 33 times moderate adverse reactions and 12 times mild adverse reactions.

Table IV. Times of adverse drug reactions (n=160).

Adverse drug reactions	Associated drugs[a]	Times (%)	Drugs ceased
Liver function damage	PAS Pto Z	26 (20.0)	Yes
Leucopenia	Rfb PAS	7 (5.4)	Yes
Kidney damage	Am Cm	5 (3.8)	Yes
Joint pain	Z	4 (3.1)	1 time yes, 3 times no
Rash	Lfx Mfx	3 (1.7)	Yes
Mental disorders	Lfx	1 (2.3)	Yes
Total		46 (35.4)	43 times yes, 3 times no

[a]PAS, p-aminosalicylic acid; Pto, protionamide; Z, pyrazinamide; Rfb, rifabutin; Am, amikacin; Cm, capreomycin; Lfx, levofloxacin; Mfx, moxifloxacin.

Discussion

The latest tuberculosis report of WHO in 2013 showed that MDR-TB patients with newly diagnosed and retreatment tuberculosis were 3.6 and 20.2%, respectively (5). The main treatment means is chemotherapy. Individualized solutions are preferred over standard ones in terms of efficacy, leading to avoidance of treatment with already resistant drugs and drugs with adverse reactions. Bastos *et al* suggested that delivering individualized treatment, according to drug sensitivity test, is significantly associated with successful treatment outcome (6). Therefore, in China in the scenario of high-burden MDR-TB, the first choice should be individualized solutions. However, the accuracy and effectiveness depend on the reliability and veracity of drug susceptibility testing in laboratory (6). In this study, the sputum mycobacterium culture, strain identification and sensitivity test report of all patients with tuberculosis in Shanghai were obtained from the Shanghai Pulmonary Hospital and Shanghai Center of Disease Control and Prevention (Shanghai, China) using BACTEC 960 the method. The quality control of the two laboratories conformed to that of the WHO standard, thus, the obtained results of drug sensitivity test were accurate and reliable, which provided assurance for individualized treatment. Patients with confirmed MDR-TB were approved through discussion of experts, to receive individualized treatment solution, with an intensive phase of 6 months. The treatment scheme included 5-6 types of anti-tuberculosis drugs, and a continuation phase of 12-18 months including 4-5 drugs. directly observed treatment, short-course (dots)-plus was implemented in the entire course of free treatment. This is a pioneer model in China and developing countries, and its advantages lie in the fact that: i) experts of MDR-TB with high authority, can formulate reasonable individualized programs; ii) free diagnosis and treatment markedly reduces the economic burden of patients, which increases their compliance for long-term treatment; iii) treatment in selected tuberculosis specialized hospital ensures standard treatment, and adverse reactions can be approached timely and properly; and iv) community health services personnel were better trained and had significant experience, and were able to implement DOT strictly.

In spite of this, we found that this treatment model only achieved a treatment success rate of 55.0%, which was lower than that established by WHO which has a set success rate of ≥75% (7). It is <60-74% than the success rate reported by other countries (8-11), similar to the success rate of 53% reported in Beijing (12), and >45-48.8% that reported by India and South Africa (13,14).

The failure rate of this study was 23.1%, the interruption rate was 11.3% and mortality 10.6%. DOT strategy can

greatly improve the compliance of patients, to ensure smooth implementation according to clinical treatment as designed by the doctor, in the background of free treatment, the interruption rate of this study was lower than that reported from South Africa (6,15), whose interruption rate was 28.7 and 21%, although there were 18 cases of interruption of treatment. Long treatment time, various drugs, adverse drug reactions, lack of proper understanding and treatment confidence for disease may lead to the interruption of treatment, and the above 18 patients were required to terminate treatment due to a variety of adverse drug reactions and did not continue to receive drug treatment. The results of treatment interruption were considered unsuccessful in that the patients became the infection source of MDR-TB, which becomes harmful to any surrounding individuals and society, and some patients may develop extensive drug resistance and pan-resistance from multidrug-resistance. As a result, doctors and DOT management personnel have th eresponsibility to provide assistance and support for these patients, and policy makers should study and investigate how to strengthen further the management of these particular patients.

The sputum mycobacterium culture test, which can reflect bacteria and infection objectively, is also used as an efficacy check. Bacteriology conversion is a reliability index used to reflect patients without infectivity (16), and a medium index can predict the success of the treatment as well (17). The sputum conversion rate of patients with MDR-TB following treatment is different at 74-92% (8,18,19) worldwide; however, early bacteriology conversion is the key to successful treatment. Our results showed that of the 58 patients who received bacterial conversion at the end of 3 months, 5 cases were identified as sputum bacterial-positive again, 1 case interrupted treatment, and the above 6 patients were capable of achieving improved efficacy when treatment was continued. The treatment cycle of MDR-TB is long, which requires taking drugs every day for ≥18 months. In the early period of treatment, patients may misunderstand that the diseases has been controlled for temporary improvement. Consequently, when designing regimen, we should consider that most patients can receive bacteriology conversion within 3 months, while, in the long term, the patients should be carefully followed up in order to maximize the success rate of treatment.

Our results suggest that retreatment, positive sputum culture mycobacterium tuberculosis for 3-month treatment, no improvement in radiography during treatment termination of treatment or permanent replacement scheme caused by adverse reaction were independent risk factors associated with poor treatment outcomes. In spite of MDR-TB bacterial strain, the success rate of initial MDR-TB patients was higher than that of retreatment as none had a history of anti-tuberculosis treatment. Thus, strengthening the drug resistance monitoring of patients with tuberculosis to identify drug resistance early and change treatment solution in a timely manner is likely to improve the success rate. Kurbatova *et al* (20) analyzed risk factors associated with poor treatment outcomes of patients with tuberculosis from countries such as Philippines and Peru. The results of those authors showed that the positive sputum culture at the end of 3 months was unsuccessful. Improvement of radiography lesion is a good index to predict the success of MDR-TB, particularly in the first 3 months.

The results of the present study showed that the presence of diabetes and termination of treatment or permanent replacement of treatment caused by adverse reactions were risk factors associated with poor treatment outcome, while XDR-TB, gender, age and scopes of lesion were not associated with treatment outcome. Falzon *et al* conducted a meta analysis (21), collecting clinical data of 6,724 patients with MDR-TB from 26 tuberculosis diagnosis and treatment centers between 1980 and 2009. The results of those authors suggested that the cure rate of MDR-TB patients who showed no resistance to fluoroquinolones and second-line injectables was higher than that of XDR-TB patients. Previous findings have identified alcohol, scope of lesions, severe clinical situation, history of second-line drugs application, and resistance to fluoroquinolones drugs were factors associated with poor efficacy (11,22,23). Sources of these unfavorable factors include long-term treatment and variety of drugs, which were significant obstacles for successful treatment. Therefore, strengthening management and improving awareness of disease is crucial. At the same time, medical workers and investigators are required to explore new short-term treatments and less variety of drugs. However, knowledge of the various confounding factors as those mentioned in this study can help clinical doctors to intervene, make a judgment of prognosis in advance, and estimate patients with bad prognosis and then adjust treatment in a timely manner.

In summary, implementing DOTS-Plus with free treatment and providing individualized type IV regimen for patients with MDR-TB in the countries with high burden of MDR-TB can moderately improve the success rate. However, the annual WHO 2015 target was not achieved. Thus, development and validation of new anti-tuberculosis drugs with better efficacy and compliance is imperative.

Acknowledgements

This study is a sponsor project of China Ministry of Health: study of simultaneous isothermal amplification and testing on tuberculosis diagnosis and treatment (grant no. W 2013RNA01).

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