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Clinical outcome of multidrug-resistant tuberculosis patients receiving standardized second-line treatment regimen in China

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ABSTRACT

Objectives: The aim of this study was to retrospectively analyze the clinical outcome and the risk factors associated with poor outcome of MDR-TB patients receiving standardized second-line treatment regimen in China.

Methods: Between January 2008 and December 2010, a total of 12,100 clinical diagnosed TB cases at high risk of drug-resistant TB (DR-TB) were enrolled in this study. Routine follow-up tests were conducted every month during the 6-month intensive phase, and every two months during the 18-month continuation phase.

Results: On the basis of phenotypical drug susceptibility test (DST) results, 2322 MDR-TB patients were confirmed, of which 1542 further received standardized second-line anti-TB regimen. The treatment success rate was 47.6% (734/1542): 688 patients (44.6%) were cured and 46 (3.0%) completed treatment. The percentage of cases with favorable outcome in previously untreated patients (57.6%) was significantly higher than that in treatment-experienced patients (46.1%, OR: 1.58, 95% CI: 1.17–2.14). In addition, a significant lower percentage of male MDR-TB cases with favorable outcome (45.8%) was observed using female MDR-TB cases as a reference (52.0%, OR: 1.31, 95% CI: 1.03–1.60). The proportion of MDR-TB cases with favorable outcome was significantly decreased in older age groups.

Conclusions: In conclusion, our data demonstrate that less than half of these patients receiving standardized second-line treatment regimen meet the definition of successful treatment during a 3-year period in China. More attention should be paid to the MDR-TB population at high-risk of poor clinical outcome, including male, elderly age, and those who have received prior treatment.

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Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampin (RIF), is a serious obstacle to TB control worldwide.[1,2] In 2015, the World Health Organization estimated 480,000 prevalent cases of MDR-TB globally, and half of MDR-TB cases occur in India, China and Russia.[1] Although the tuberculosis prevalence of China has been halved from 1990 to 2010,[3] a national survey of drug-resistant TB conducted in China revealed that 5.7% of previously untreated and 25.6% of previously treated cases had MDR-TB, respectively.[4] The strikingly high incidence of MDR-TB in China represents an obvious threat to the progress that has been made in the control of TB over the past decades.[4]

Due to resistance to backbone drugs in the first-line TB regimen, the treatment of MDR-TB requires more expensive and more toxic second-line drugs, while the clinical outcome of MDR-TB is generally unsatisfactory.[5,6] Despite treatment success rates of 60%–70% reported by several published studies,[7,8] a meta-analysis has demonstrated that only 48% of MDR-TB cases who started treatment achieved a favorable outcome worldwide.[9] The poor clinical outcomes among MDR-TB patients reflect a strong global need to develop new anti-TB drugs.[10] Recently, many promising new anti-TB drug candidates have entered the drug pipeline owing to international public health efforts,[10] while the incredibly high cost and limited accessibility of these new candidates makes the treatment of MDR-TB cases mainly depend on traditional second-line drugs under current settings.[11]

China faces a dire MDR-TB challenge – China as the second highest MDR-TB burden in the world and because of the low coverage of drug susceptibility testing (DST), only 17% of MDR-TB patients were

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detected.[1,12] In addition, the unavailable DST results make it difficult to design personalized treatment regimens for these patients, and the standardized second-line regimen has been used following the guidelines endorsed by WHO.[13] Despite the urgent need, we still lack national data regarding the efficacy of standardized second-line regimen for treating MDR-TB patients in China. In 2008, under support from Global Fund, a national project was conducted in China to improve MDR-TB detection and treatment. The aim of this study was to retrospectively analyze the clinical outcome and the risk factors associated with poor outcome of these patients.

Materials and methods

Ethics statement

The study was approved by the Ethics Committee of Chinese Center for Disease Control and Prevention. All patients provided written informed consent before they were included in this study.

Patients

Between January 2008 and December 2010, a total of 12,100 clinical diagnosed TB cases at high risk of drug-resistant TB (DR-TB), who sought health care in TB dispensaries of Inner Mongolia, Shandong, Henan, Hubei, Zhejiang, and Guangdong, were enrolled in this study. The patients met the following criteria: (1) retreatment patients who failed to respond to the initial regimens for retreatment cases; (2) new patients who failed to respond to the initial regimens for new cases; (3) patients with reported history of contact with DR-TB cases; (4) patients who had positive sputum smear results by the end of first-line anti-TB regimen, were defined as TB cases at high risk of drug-resistant TB. Two specimens were collected from each participant for solid culture. Among 11,801 patients, 3094 (26.2%) and 83 (0.7%) patients were excluded for negative culture and contamination during culture process, respectively. As a consequence, 8624 positive cultures were delivered from county-level laboratories to prefecture-level laboratories for conventional DST examination. On the basis of phenotypical DST results and stains identification, 2332 MDR-TB patients were confirmed, of which 1542, providing signed informed consent, further received second-line anti-TB regimen, whereas 289 patients refusing to participate and 251 patients infected with NTM were excluded from this study, respectively (Fig. 1).

Laboratory exanimation

Direct smears of each sputum specimen were performed using Ziehl–Neelsen (Z–N) staining for acid fast bacilli (AFB).[14] The residual specimen was digested with N-acetylcysteine-sodium hydroxide (4%) for 15 minutes, and inoculated onto Löwenstein–Jensen (L–J) medium as previously reported.[15] Bacterial colonies were collected four to eight weeks later for conventional DST and identification. The proportional method was used for determining the susceptibility of MTB isolates against RIF and INH. The concentrations of drugs in media were following the guidelines from WHO: RIF 40 μg/ml and INH 0.2 μg/ml.[16] The strain was declared as resistant to the drug if the growth rate was more than 1% compared with the control. The MDR strains were defined as strains resistant to both RIF and INH.

Treatment and follow-up

Before the patients were diagnosed as MDR-TB by conventional DST, they received the first-line regimens recommended by the National Tuberculosis Programme (NTP) treatment guidelines. Treatment of new patients consisted of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifampicin (2HREZ/4HR). Retreatment patients received 2 months of isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol, followed by 6 months of isoniazid, rifampicin, and ethambutol (2SHRZE/6HRE). The MDR-TB patients enrolled in this study received a standardized treatment regimen, consisting of a six-month intensive phase (eight months if sputum was positive at six months), followed by an 18-month continuation phase: 6 Z, Am(Cm), Lfx (Mfx), Cs(PAS, E), Pto/18 Z, Lfx (Mfx), Cs (PAS, E), Pto) (Am, amikacin; Cm, capreomycin; Cs, cycloserine; E, ethambutol; Lfx, levofloxacin; Mfx, moxifloxacin; PAS, p-aminosalicylic acid; Pto, protionamide; Z, pyrazinamide). Prior to initiating treatment, the demographic characteristics and medical history were collected from each patient. Patients commenced treatment through hospitalization for up to two months. After the hospitalization period, patients completed the subsequent treatment under direct observation by

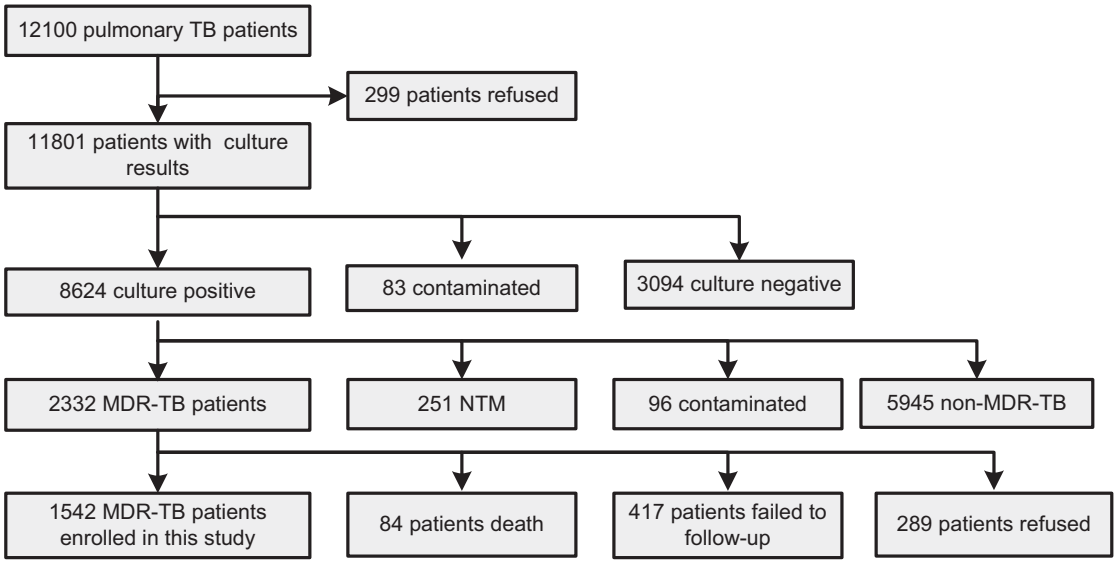

Fig. 1. Enrollment of MDR-TB patients in this study.

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