Original Article

Clinical profile and treatment outcomes of drug-resistant tuberculosis before directly observed treatment strategy plus: Lessons for the program

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ABSTRACT

Background: Characteristics and treatment outcomes of patients with drug-resistant tuberculosis (DR TB) before introduction of directly observed treatment strategy (DOTS) plus are infrequently reported. **Aims:** To study clinical characteristics and treatment outcomes of drug-resistant TB patients. **Setting:** A TB unit in Mumbai. **Materials and Methods:** A retrospective analysis of DR TB patients attending a TB unit and taking treatment at NGOs was performed. Of the 34 cases, 5 (14%) had mycobacterium other than tuberculosis, 24 were pulmonary TB, 4 extra-pulmonary TB, and one both. Three were HIV-infected, two had diabetes. Two cases were treatment naive. Of the 29 cases studied, 3 (11%) were mono-resistant, 20 (69%) were multidrug-resistant (MDR) TB with E/Z/EZ resistance; 4 were pure MDR TB. One case had XDR TB, 13 (44.8%) had resistance to at least one conventional second-line drug. Seven cases had adverse drug reaction, four requiring drug substitution. Two patients are on treatment; 14 of the remaining 27 (51%) were successfully treated, 5 (18%) died, 2 (7%) failed treatment, 5 (18%) were lost to follow-up, one migrated. **Conclusion:** DST profiles suggest high levels of drug resistance due to amplification which leads to poor outcomes. There is an urgent need for Indian Revised National TB Control Program to introduce daily DOTS for susceptible cases, DST for all new cases, and scaling up DST for second-line drugs. There is also a need to use individualized treatment for DR TB.

KEY WORDS: Amplification of resistance, daily directly observed treatment strategy, individualized treatment, scaling up DST for second-line drugs

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INTRODUCTION

Drug-resistant tuberculosis (DR TB) has been known since the first introduction of chemotherapy for TB and has become a high priority for TB control programs in recent years. Programmatic management of drug-resistant TB (PMDT) is being implemented in India in a phased manner since 2006. Around 99,000 cases of multidrug-resistant TB (MDR TB) are estimated to occur annually and in need for treatment.[1]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.120608

In Mumbai, high levels of DR TB have been reported among patients attending Revised National TB Control Program (RNTCP) facilities.[2] Before the introduction of PMDT in Mumbai in July 2010, patients from the program who were suspected having DR TB were being diagnosed and treated with support of NGOs.

A study to document the role of NGOs in managing DR TB was undertaken in Mumbai (unpublished). Data of patients were reviewed to determine their characteristics and outcomes. The study was approved by the institutional ethics committee.

We report a retrospective analysis of a cohort of DR TB patients attending one tuberculosis unit (TU) from Mumbai before the introduction of PMDT and being treated at NGO clinics.

MATERIALS AND METHODS

Setting

The TU in KS ward in Mumbai is a unique example of private public partnership with a corporate body supporting the local RNTCP with a chest physician and a counsellor. The TU gets referrals from the regional peripheral health institutions and private providers.

Before July 2010, patients failing RNTCP category 1 or category 2 regimen and those referred from private sector were assessed thoroughly. Sputum culture for acid fast bacilli (AFB) and drug susceptibility testing (DST) were carried out for all first- and second-line drugs (FLDs and SLDs) including kannamycin, amikacin, capreomycin, ethionamide, paraamino salicylic acid (PAS), ofloxacin, moxifloxacin, and clofazimine, based on prior drug history, at either the Sir J. J. Hospital laboratory or the Hinduja Hospital. Cases with extra-pulmonary TB (EPTB) were subjected to tissue biopsy and culture DST at the Hinduja Hospital. Both laboratories are accredited by RNTCP for liquid culture and DST for FLDs and line probe assay for MDR TB plus; additionally, Hinduja Hospital laboratory is accredited for Mycobacterial growth indicator tube (MGIT) culture and FLD and SLD DST by the College of American Pathologists. DST was performed by MGIT liquid culture for both FLDs and SLDs. WHO critical concentrations were used as applicable for susceptibility testing to both FLDs and SLDs. H37Rv strain is used for both culture and susceptible TB and a fully characterized isolate that has high level mutations for resistant TB are used as control strains.

Definitions

Monoresistance is defined as resistance to any one anti-TB drug, polydrug resistance is resistant to more than one drug but not MDR; MDR is defined as resistance to at least isoniazid (INH) and rifampicin (RMP); patients who did not have resistance to INH and RMP were labelled non-MDR. Pre-XDR was MDR with additional resistance to either one of the fluoroquinolones or injectable aminoglycosides, extensively drug resistant TB (XDR TB) was MDR with additional resistance to both fluoroquinolones and injectable aminoglycoside.

Routine investigations to rule out diabetes mellitus, hepatic and renal diseases, screening for HIV at Integrated Counselling and Testing Centre, and chest X-ray were done at baseline.

Treatment

Pending culture and DST results, patients were initiated on empiric domiciliary treatment with SLDs based on a detailed prior drug history. On receipt of the DST results, treatment was modified if required. Patients were counselled and guided to NGOs for subsidized or free treatment and advised to return for regular follow-up examinations.

Clinical and sputum smear examinations for AFB were carried out at monthly intervals for initial 6 months and every 3 months thereafter. X-rays were taken every 3 months. The initial intensive phase was for 3-6 months till sputum smear conversion and continuation phase till 1 year to 18 months after sputum smear conversion was achieved. Cultures were not done as a routine to monitor therapy. In very few cases was culture repeated where the patient was willing to spend or there was clinical indication to rule out further resistance.

Monitoring for drug-related adverse events was done clinically. Blood investigations were carried out when required. Audiometry, ophthalmic examinations, and psychiatric assessment were carried out whenever necessary. For this purpose, the patients were referred to tertiary centres. Hospitalization, if necessary, was done at the group of TB hospitals, Sewri.

Data and analysis

Patient data were recorded on a MDR TB case card. Data were entered on SPSS 16 and cross-checked. Chest x-rays were read by the chest physician and recorded.[3] Clinical, bacteriological, and radiological characteristics were analyzed using descriptive statistics, frequencies and cross tabulations. Outcomes were defined as per the National guidelines.[4]

RESULTS

A total of 34 cases of DR TB were enrolled for treatment during the period August 2006 to November 2010. Majority of the cases were in the age group 15-35 years (23/34-67.6%)-mean age was 31 (range: 15-61 years) with a male to female ratio of 1:1, half of the patients were married. Five of 34 (four males and one female) had no education. One-fourth of the males were unemployed and one-fourth of females were in employment [Table 1].

Comorbidities

Three cases were detected to have HIV1 co infection [one had infection with mycobacterium other than tuberculosis (MOTT)]; two cases had diabetes and were on treatment.

Cultures

A total of 5 of the 34 (14%) samples grew MOTT and were excluded from subsequent analysis. A total of 29 cases were studied.

Previous treatment history

Prior to diagnosis of DR TB, two patients had no treatment for tuberculosis, 27/29 had at least one course with FLDs-12 had taken from RNTCP, 13 from private and in 2 the source of treatment was not known. Outcome of this treatment was 8 cured, 10 failed (two failure cases had been started on SLDs before being enrolled), and 3 defaulted. Two cases had been on SLDs before being enrolled. 14/27 had a second course of treatment with FLDs-all received category 2 treatment from RNTCP, 12 failed and 2 were cured.

Table 1: Baseline characteristics of drug-resistant tuberculosis patients enrolled

Number of patients with DST enrolled	**34**		
Speciation			
MOTT	5 (excluded)		
M. Tb	29 (included)		
Demographic			
Age group	Male	Female	
15-35 years	10	13	
36-55 years	5	4	
56-69 years	2	0	
Education			
Nil	4	1	
Primary school	9	6	
Higher school	3	9	
Graduate	0	1	
Postgraduate	1	0	
Occupation			
Unemployed	4	3	
Household work	0	8	
Retired	3	0	
Laborer	3	1	
Service	1	3	
Skilled worker	4	0	
Student	1	2	
Marital status			
Never married	10	7	
Married	6	9	
Widowed	0	1	
TB drug history			
Nil	2		
	RNTCP	Private	Not known
First-line drugs (FLDs)-one treatment	12	13	2
FLDs-more than one treatment	14	0	0
Second-line drugs (SLDs)	0	2	0
Site of disease			
Pulmonary (PTB)	24		
Extrapulmonary (EPTB)	4		
PTB + EPTB	1		

MOTT: mycobacterium other than tuberculosis, TB: tuberculosis

Site of TB

A total of 24 of 29 had pulmonary (PTB), 4/29 had EPTB all lymph node involvement and 1/29 had both PTB and EPTB (sternal osteomyelitis with ulceration).

Radiological features

A total of 20 of the 25 PTB cases had cavitary lesions, 13 single and 7 more than one cavity; 14 cavities were unilateral and 6 bilateral. A total of 20 of the 25 PTB cases had moderate to extensive lesions on x-rays.

DST profile

FLD susceptibility

A total of 3 out of 29 (11%) patients were mono-resistant, 20 (69%) were MDR with Z/E/ZE resistance, there were 4 (14%) pure MDR, and 2 (6%) were resistant to more than one drug except H&R (poly-resistant).

There were four (14%) pre-XDR TB and one (3%) was XDR TB.

Five MDR TB cases had resistance to at least one group 5 drug.

Resistance to conventional SLDs

In all 13 (44.8%) (eight MDR TB, three mono-resistant, and two poly-resistant) cases were resistant to at least one conventional second line drug, that is, ethionamide, PAS, or cycloserine.

Of the two patients who had taken SLDs before enrolment, one was mono-resistant to FLD and had resistance to at least one SLD; the other was MDR with resistance to at least one SLD.

Drug susceptibility was done on an average for 12 drugs (4-16); resistance was seen to an average of 7 drugs (3-16) with an average resistance rate of 58% (23-100%). Four cases had resistance to 100% tested drugs. One case was resistant to all 16 of the drugs tested and can be considered totally drug resistant (TDR) as reported by other researchers.[5,6]

Sputum smear conversion took on an average 7.8 months (earliest 3 months and latest 11 months). One diabetic patient converted at the 4th month and deteriorated later due to inadequate doses and failed treatment (was culture positive).

Adverse drug events

A total of 7 of the 29 cases receiving SLDs had adverse drug events during the course of treatment. In four cases, the offending drugs had to be discontinued and substituted (three had psychiatric problems due to cycloserine, one developed a large goitre due to PAS); one had severe tendinitis due to levofloxacin and two patients who had gastrointestinal intolerance were managed with supportive treatment.

Treatment outcomes

Two patients are still on treatment at the time of analysis. One of them is the TDR TB case who is on salvage therapy and currently sputum smear negative. A total of 14 of the remaining 27 (51%) were successfully treated, 5 (18%) died, 2 (7%) failed treatment, 5 (18%) were lost to follow-up, and 1 migrated out of the city [Table 2].

Successfully treated patients were followed-up clinically and by smear studies for an average of 2.4 years (range: 0-4.5 years). So far, none of them have recurrence or any clinical evidence of respiratory disability.

DISCUSSION

A total of 67% of our DR TB cases were young (15-35 years) compared to 44% suspected cases from Andhra Pradesh.[7] It is important to note that around 14% of the group had

Table 2: Showing treatment outcomes* for various resistant patterns#

Susceptibility pattern	Cured	Failed	Died	Lost to follow up	Transfer out	Total
Mono-resistant	1	0	0	1	1	3
HR resistant	2	0	1	0	0	3
HR+Z/E/ZE resistant	9	2	4	4	0	19
Poly-resistant (non-MDR)	2	0	0	0	0	2
Pre-XDR	2	1	1	0	0	4
XDR	1	0	0	0	0	1
Resistant to any group 5 drug	1	1	0	1	0	3
Resistant to any conventional SLD	5	1	2	4	1	13

*Two cases are on treatment, #Total more than cohort as cases included in more than one pattern

EPTB in the form of lymph node involvement. Currently, the directly observed treatment strategy plus program does not enrol EPTB patients for treatment. Around four-fifth of the MDR TB patients had moderate to extensive shadows and had cavities on chest X-rays. This has also been reported in a cohort of MDR TB patients from Mumbai.[3]

Pulmonary infections due to MOTT are increasingly being reported in recent times.[8] Our cohort had 14% MOTT cases. These need susceptibility testing to other drugs, do not pose a public health threat, and thus there are no guidelines for their management. A high level of suspicion is needed to identify these cases which masquerade as DR TB.[9]

In India, the RNTCP follows the thrice weekly treatment for DOTS under category 1 and 2. Acquired resistance to RMP is reported to be three times more common when INH and RMP are administered thrice weekly compared to daily.[10] There is an increased risk of failure, relapse, and acquired RMP resistance when intermittent regimens are used.[11] Also category 2 has been shown to have poor outcomes in retreatment of patients failing category 1 treatment[12] and is unacceptable as it adds only one drug-streptomycin to the failing four drugs.[13] In a study from Mumbai, the proportion of resistance to three or more drugs including HR (20%) was greater than that of resistance to HR only (4%).[3] This, along with our observation of twenty of the 24 MDR TB patients having resistance to other first line drugs, suggests a probable amplification of resistance by category 2 treatment which was the treatment for 14 of our cases under RNTCP. There is, thus, an urgent need for Indian RNTCP to revise its guidelines for management of TB on lines of the WHO recommendation of daily DOTS[14] and as per recommendations by the Joint Monitoring Mission 2012 (Fraser Wares-personal communication) do away with the category 2 regimen for failures and to detect DR TB early by subjecting all new cases of TB to culture and DST.

Our cohort had around 13% pre-XDR TB and 3% XDR TB; around a fifth of the MDR TB cases had resistance to one of the group 5 drugs and resistance to conventional SLDs of 44%. One of our cases was found to be resistant to all the 16 drugs to which the DST was performed and thus could be classified as a TDR TB case. Thus, the DR scenario in Mumbai seems to be grim as there are many patients with amplified drug resistance. There is an urgent need to scale up accreditation of laboratories for SLD susceptibility testing and offering the tests to all suspected DR TB cases, so that appropriate therapy is instituted early to prevent further drug resistance from developing.

Treatment outcomes in the face of high levels of resistance to SLDs are poor.[15] Use of standard treatment regimen for managing DR TB in a scenario of such high levels of resistance will lead to poor outcomes and only fuel the DR TB epidemic. There is, thus, an urgent need to review the current treatment guidelines for MDR TB and consider introduction of individualized treatment which has been successfully implemented in Peru.[16,17]

Adverse drug reactions occurred to the tune of 24% in our cohort, in half of these cases the offending drug had to be substituted. None of the patients required hospitalization. This incidence is very low compared to that reported in HIV/MDR TB co-infected patients, wherein 71% of cases had at least one adverse event during therapy.[18]

Treatment outcomes: Our treatment success of 51% compares well with 53.4% reported for MDR TB cases from China,[19] 66.2%-70.2% from Latvia,[20] 70% from Nepal[21] and 66% from Chennai.[22] Deaths were higher in our cases compared to 3% and 6.3% among MDR TB and XDR TB cases reported from China,[19] 8% from Nepal[21] and Chennai.[22] Our lost to follow-up (18%) and failure (7%) were comparable to 13% each that reported from Chennai[22] and 17% and 5% that from Nepal.[21] Treatment outcomes of DR TB without comorbid conditions are better than those reported for a cohort of HIV-infected MDR TB patients from Mumbai who were also on antiretroviral treatment.[23]

Resistance to SLDs is associated with high-failure rates.[15] In our study, of the 13 patients who had resistance to SLDs, five (38%) had successful outcomes; there was one failure and two deaths-3(23%); four were lost to follow up and one migrated [Table 2].

A major limitation of this study is that the laboratories were not accredited for DST to SLDs by the RNTCP. Both laboratories, however, had systems for external quality assurance of their results. Another limitation was the inability to monitor patients with culture. We, therefore, could not have any "cured" case as our outcome. A study reported from a DOTS plus site in India has suggested the use of periodic sputum smears as surrogate to culture reports;[24] however, although this could have given a false impression of "early conversion" and apparently shortened the duration of infectiousness, it could have missed out on detecting failures early.[25] The small size of

the cohort could have resulted in overestimation of certain parameters. Limitations notwithstanding, the findings bring to fore the need to re-evaluate the current strategies and policies and take corrective measures in the TB control program in India.

CONCLUSION

DST profiles suggest high levels of drug resistance due to amplification which leads to poor outcomes. There is an urgent need for Indian Revised National TB Control Program to introduce daily DOTS for susceptible cases, DST for all new cases, and scaling up DST for second-line drugs. There is also a need to use individualized treatment for DR TB.

ACKNOWLEDGMENT

The authors wish to thank the various NGOs and individuals who supported the treatment of the DR TB cases either free or at subsidized cost and the RNTCP staff of the TU for providing follow-up of the patients. Dr. Camilla Rodrigues-Consultant Microbiologist, P. D. Hinduja National Hospital performed free bacteriology studies for identifying atypical Mycobacterial infections.

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How to cite this article: Dholakia YN, Shah DP. Clinical profile and treatment outcomes of drug-resistant tuberculosis before directly observed treatment strategy plus: Lessons for the program. Lung India 2013;30:316-20.

Source of Support: Nil, **Conflict of Interest:** None declared.