Original Article

MANAGEMENT OF MULTI DRUG RESISTANCE TUBERCULOSIS IN THE FIELD: TUBERCULOSIS RESEARCH CENTRE EXPERIENCE

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Summary

***Setting*:** Multi-drug TB resistant (resistant to isoniazid and rifampicin) patients identified from a rural and urban area.

***Objective*:** To study the feasibility of managing MDR TB patients under field conditions where DOTS programme has been implemented

***Methods*:** MDR TB Patients identified among patients treated under DOTS in the rural area and from cases referred by the NGO when MDR TB was suspected form the study population. Culture and drug susceptibility testing were done at Tuberculosis Research Centre (TRC). Treatment regimen was decided on individual basis. After a period of initial hospitalization, treatment was continued in the respective peripheral health facility or with the NGO after identifying a DOT provider in the field. Patients attended TRC at monthly intervals for clinical, sociological and bacteriological evaluations. Drugs for the month were pre-packed and handed over to the respective center.

***Results*:** A total of 66 MDR TB patients (46 from the rural and 20 from the NGO) started on treatment form the study population and among them 20 (30%) were resistant to one or more second line drugs (Eto, Ofx, Km) including a case of "XDR TB". Less than half the patients stayed in the hospital for more than 10 days. The treatment was provided partially under supervision. Providing injection was identified to be a major problem. Response to treatment could be correctly predicted based on the 6-month smear results in 40 of 42 regular patients. Successful treatment outcome was observed only in 37% of cases with a high default of 24%. Adverse reactions necessitating modification of treatment was required only for three patients.

Implications Despite having reliable DST and drug logistics, the main challenge was to maintain patients on such prolonged treatment by identifying a provider closer to the patient who can also give injection, have social skills and manage of minor adverse reactions. ***[Indian J Tuberc 2007: 54: 117-124]***

Key words: MDR-TB management, RNTCP, field experience

INTRODUCTION

One of the major threats to TB control is the emergence of drug resistant TB, particularly multi-drug resistant TB (MDR TB) – TB strains resistant to Isoniazid and Rifampicin. Of the 424,203 MDR-TB cases estimated world-wide by the WHO, more than half the cases are estimated to be in China and India[1]. Identifying this problem, the Revised National Tuberculosis Control Programme (RNTCP) in India, is planning to introduce DOTS-Plus services into the programme for the management of MDR-TB patients. There are several reports on the management of MDR-TB in the field,[2-9] but limited information is available from India.

The Tuberculosis Research Centre (TRC), Chennai has been monitoring the RNTCP DOTS programme in a rural area [10] and giving technical support to an NGO implementing RNTCP in the city of Chennai in the southern part of India. As a part of operational research activities, TRC, with its well established myco-bacteriology laboratory, recognised as a National Reference Laboratory of RNTCP and as a Supra-national Reference Laboratory of the WHO, has been monitoring drug susceptibility profile (DST) of all patients registered for treatment in the rural area and for chronic cases referred by the NGO. DST included both first and second line drugs. Patients identified to have MDR TB were referred to TRC for further management. This paper describes the experience of management of MDR-TB patients under field conditions and also our observations on extensively drug-resistant TB (XDR-TB, see

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footnote[1]) in this group of patients.

MATERIAL AND METHODS

Setting

The study area is a sub-district (predominantly rural) of Tiruvallur district, in south India, with population of 580,000 where RNTCP was implemented in May 1999 and TRC was monitoring the DOTS programme. The area has 17 governmental health care facilities, including 7 designated microscopy centers. From this study area, during 1999-2003, 4467 patients were registered and among them 2206 had positive cultures. Of these 81 were identified as MDR-TB and 48 initiated on treatment. One patient had XDR pretreatment.

A non-governmental organization working in Chennai city involving the private sector to support RNTCP also referred. 35 patients of suspected to have MDR-TB and 20 were initiated on treatment.

Study population

MDR-TB patients identified from the two areas and referred to TRC for management during May 1999 to December 2003 form the study population.

Pre-treatment Investigations

Procedures for sputum culture and drug susceptibility testing

For all tuberculosis patients registered for treatment under RNTCP in the rural area, two additional sputum samples were collected within one week of starting treatment, if a patient became smear-positive during treatment, and at 12, 18 and 24 months from all cured patients as an operational research activity. The NGO in Chennai city referred patients with suspected MDR TB and two sputum specimens were collected at TRC. All specimens were processed at TRC for culture and drug susceptibility testing. Sputa were collected in sterile McCartney bottles containing cetyl pyridinium chloride (CPC) [11] provided by TRC. If missed, TRC field staff visited the patients' homes and collected sputa within a week. Sputum was also collected at 12, 18 and 24 months by TRC field staff as part of an operational study to assess relapse[12]. All specimens were subjected to culture for *M.tuberculosis* and drug susceptibility testing for Isoniazid (H), Rifampicin (R) and Streptomycin (S) on Lowenstein Jensen medium (LJ medium)[13]. Concentrations of H, R and S used were 0.2, 1, 5; 32, 64, 128; and 8, 16, 32, 64 mg per litre respectively. The resistance to H and R was determined by minimal inhibitory concentration (MIC) and to S by Resistance Ratio (RR) methods[14]. MIC of 1mg/litre or more and MIC of 128mg/litre or more, were defined as resistance for H and R respectively and an RR of 8 or more was considered as resistance to S[15]. DST was done for Kanamycin (K), Ethionamide and Ofloxacin at the time of starting treatment for MDR-TB by MIC methods. The concentrations of Ofloxacin used were 2, 4, 8 for Kanamycin 8, 16, 32 & 64 and Ethionamide as 20, 28, 40, 57, 80 and 114. MIC of and of $\geq$8 for Ofloxacin, $\geq$64 for Kanamycin and $\geq$114 for Ethionamide were considered as resistance. DST to second line drugs was done based on the drugs patients were treated with.

Other investigations

Patients identified to have MDR-TB were referred to TRC, Chennai for further management. Prior to starting treatment all patients underwent detailed clinical, sociological and bacteriological evaluations. In addition, chest radiograph, hepatic and renal function tests and complete haemogram were done. HIV testing was done after initial counseling and obtaining informed consent.

Treatment regimen

Patients were started on treatment on an individual basis, primarily based on the drug

[1]XDR-TB is defined as resistance to at least Rifampicin and Isoniazid (which is the definition of MDR-TB), in addition to any fluoroquinolone, and to at least one of the three following injectable drugs used in anti-TB treatment: Capreomycin, Kanamycin and Amikacin.

susceptibility profile. The regimens used were:

Group I: $6Sm_3$ / Km_3 Ofx Eto Z E daily followed by 12 Ofx Eto Z E daily

Group II: Other combinations for eg. $6Sm_3$ / Km_3 Ofx Eto Z H high dose daily followed by 12 Ofx Eto Z H daily

$6Sm_3$ / Km_3 Ofx Z E with Cs/PAS/High dose INH daily followed by 12 months of oral drugs etc.

Drugs and dosage:

Streptomycin (Sm)	0.75 gm thrice a week
Kanamycin (Km)	1.00 gm thrice a week
Ofloxacin (Ofx)	400–600 mg daily
Ethionamide (Eto)	500 mg daily
Ethambutol (E)	800 mg daily
Pyrazinamide(Z)	1.5 gm daily
PAS	10 gm daily
Cycloserine (Cs)	500mg daily
Amikacin (Am)	1 gm daily
Isoniazid (INH)	600mg daily

Duration of treatment

Patients received all the five drugs for the initial 6-month period. During the next 12 months the injection was stopped and treatment continued with oral drugs. The total duration of treatment was for a minimum period of 18 months or 12 months after the culture negativity whichever came later.

Patient management

After initiation of treatment, the patients were advised hospitalization in one of the TB hospitals in Chennai city for a minimum period of one month to monitor the drug tolerance. On discharge from the hospital, clinical, bacteriological and sociological assessments were done at TRC and patients were advised to attend the respective Primary Health Centre (PHC) / NGO for continuation of treatment. Drugs for one week were supplied to the patient to ensure continuity of treatment during the transit period. The patients were transferred to the PHC Medical Officers / NGO for continuation of treatment. Details of the chemotherapy prescribed and dates for further assessment were intimated through a referral letter. A DOT provider was identified for administering drugs under direct observation. These providers were given on the spot training for drug administration and adverse reactions to be anticipated and the action to be taken. Patients received the treatment under partial supervision i.e. thrice-a-week when patients attended for injection, oral drugs were given under supervision and the next day's dose was supplied for self administration. The same procedure was followed after the injection phase was completed.

Clinical assessment and sociological counseling were done every month at TRC. Reminders were sent to the patients one week prior to the due date for monthly checkup. During these monthly follow-ups, an early morning and spot sputum specimens were examined by smear and culture for *M. tuberculosis*. For all patients financial assistance to compensate for the loss of wages and travel expenses on the day of attendance to TRC was given.

Drug Logistics

Drugs were provided by TRC as there was no provision for second line drugs in the field. During the period of hospitalization, TRC health worker supplied the drugs to the hospital staff on alternate days. After discharge, patients continued treatment at their respective PHCs/private providers or TRC clinic where they received the drugs from a DOT provider. Pre-packed drugs (each dose in a separate packet) were supplied to the respective PHC/NGO on a monthly basis, following the patient's monthly follow-up visit at TRC. Patients attended on alternate days to receive the drugs under observation and the next days drugs were supplied for self-administration i.e. treatment was given under partial DOT.

Definitions of treatment outcomes

Cured: A patient who has completed treatment for at least 18-months and has been culture negative for the final 12 consecutive months of

treatment.

Death: A patient who dies during the course of treatment.

Failure: A patient who remains culture-positive at 6 months or those who become consistently positive subsequently during treatment and require change of treatment.

Default: A patient who had interrupted treatment for two or more consecutive months.

RESULTS

In all 68 (48 from the Tiruvallur area and 20 from Chennai city) patients were started on treatment for MDR-TB. Of the 48 patients started on second line drugs from Tiruvallur area, 2 patients were subsequently excluded (one patient had organisms sensitive to Rifampicin and other negative culture at the time of initiation of treatment for MDR-TB) – hence analyses was done on 66 MDR-TB patients.

The demographic profile of patients is described in Table 1. Of 66 patients, 70% were males; the mean age was 38 years (range 14-75) and mean weight was 42.7 kg (range 23.2–60.5). Of the 66 patients, 7 had received less than 6-months of prior treatment, 27 6-9 months, and 32 more than 9 months. All patients had received treatment with either CAT-II and/or CAT-I regimen under RNTCP.

Table 1: Demographic profile of patients on treatment for MDR TB

Total patients	66
Males	46
Median age in years (range)	37 (14-75)
Median weight in kg (range)	42.2 (23-60)
Duration of prior treatment	
<6 months	7 (10.6%)
6-9 months	27 (40.9%)
>9 months	32 (48.5%)

Table 2. Drug susceptibility profile at the time of initiation of MDR-TB treatment

Resistant to		No (66)	%
2 drugs	HR	12	18
3 drugs	HR S	17	26
	HR E	6	9
	HR Ofx	1	2
	HR Eto	2	3
4 drugs	HR S E	11	17
	HR S Ofx	1	2
	HR S Eto	5	8
	HR E Eto	3	5
5 drugs	HR S E Eto	5	8
	HR S Km Eto	1	2
6 drugs	HR S E Eto Ofx	1	2
7 drugs	HR S Km E Eto Ofx	1	2

S=Streptomycin, Km=Kanamycin, E=Ethambutol, Eto=Ethionamide, Ofx=Ofloxacin, H=Isoniazid, R= Rifampicin

Drug sensitivity pattern

At the start of treatment twelve (18%) patients had organism resistant only to HR, 34 (52%) resistant to one or two of the first line drugs in addition to HR (S/E), and the remaining 20 (30%) were resistant to one or more second line drugs (Eto, Ofx, Km) in addition to HR (Table 2). Of 33 patients for whom DST results for Km and Ofx are available, one had organism resistant to both Km and Ofx in addition to HR, i.e. was a case of extensive drug resistant TB – "XDR-TB".

Patient management

Of the 66 patients, 30 were not admitted to the hospital and another 10 stayed in the hospital for less than 10 days. The main reasons were: not able to stay away from work and the distance to the hospital from their residence. In the rural area the DOT provider identified was mainly anganwadi workers. Patients received injections either from the village health worker whenever available or from a private provider by paying or went to the primary

Table 3: Treatment outcome of the MDR TB patients according to the resistance pattern

Resistant to	No. of patients	Cured	(%)	Failure	(%)	Default	(%)	Death	(%)
HR	12	5	(41.6)	2	(16.7)	4	(33.4)	1	(8.3)
SHR/HER/SHRE	34	12	(35.3)	9	(26.5)	8	(23.5)	5	(14.7)
HR + other Drug(s)	20	8	(40.0)	6	(30.0)	4	(20.0)	2	(10.7)
Total patients	66	25	(37.8)	17	(25.7)	16	(24.3)	8	(12.2)

health center. The urban patients took treatment either at TRC clinic or from the nearby private hospital or a practitioner involved in the RNTCP.

Treatment outcome

Of the 66 patients, 25 (38%) patients were 'cured', 17 (26 %) failed, 16 (24%) defaulted and 8 (12 %) died during treatment (Table 3). The outcome with respect to regimens I (46 patients) and II 20 patients) were: cure 19 (41%) vs 6 (30%), failure 14 (30%) vs 3 (15%), default 10 (22%) vs 6 (30%), death 3 (7%) vs 5 (25%) (Table 4). The difference in cure was not statistically significant. Treatment outcome was not related the duration of prior chemotherapy received.

Treatment outcome related to resistance pattern

Among the 12 patients with HR resistance, 5 were cured, 2 failed, 4 defaulted and 1 died (Table 3). Among the 34 patients with resistance to HR + S/E, 12 (35%) cured, 9 (26%) failed, 8 (24%) defaulted and 5 (15%) died. Of the 20 patients who had resistance to second line drugs in addition to HR, 8 (40%) were cured, 6 (30%) failed, 4 (20%) defaulted and 2 (10%) died. These differences were not statistically significant.

Culture conversion among cured patients

Among 25 patients cured, culture conversion occurred at first month for 8 (40%), at 2 months for 6 (30%), 3 months for 2 (10%), at 4 months 2 (10%) and 1 (5%) patient each at 5 and 9 months. Overall 14 (70%) converted by 2 months and 18 (90%) converted by 4 months. All except two cured patients had smear conversion also by 3rd month and all failures were smear-positive at 3rd month.

Status of defaulters and failures

Of the 16 patients who had defaulted, treatment was resumed for eight patients, three had died and the remaining five continued to default. Default was attributed to be due to adverse drug reactions by four patients. Among 17 failures, 2 died. Treatment was changed for the remaining 15 patients, two patients defaulted and of the remaining 13 patients, five patients are responding to the new treatment. One patient who was resistant to SmHRKmEEto emerged resistance to Ofx and another patient who had resistance to SmHREEto emerged resistance to Km and Ofx i.e. 2 patients developed XDR-TB resistance during treatment.

Table 4: Treatment outcome of the MDR TB patients according to the treatment regimens

Regimen	No. of pts	Cured	(%)	Failure	(%)	Default	(%)	Death	(%)
Tiruvallur area	46	19	(41.3)	14	(30.4)	10	(21.7)	3	(6.6)
Chennai city	20	6	(30.0)	3	(15.0)	6	(30.0)	5	(25.0)
Total Pts	66	25	(37.8)	17	(25.0)	16	(24.3)	8	(12.2)

Sputum status at 6 months

All the 25 patients with negative smears for AFB at 6-months of treatment had a favourable response (cure) Among the 17 failures, 16 were smear-positive at 6-months.

Adverse drug reaction

Of the 66 patients, 39 (59%) had adverse reactions, among these 26 (67%) gastrointestinal, 7 (18%) skin, 5 (13%) giddiness, 3 (8%) had insomnia and only one patient had jaundice. However Ethionamide had to be withheld in only one patient and two patients were managed by changing to enteric coated Ethionamide tablets. All drugs were withheld for three weeks for the patient who developed jaundice, and treatment was reintroduced and continued without any further problem.

DISCUSSION

The main finding of our study was that of the 66 MDR TB patients treated cure was observed only amongst 38%, despite ensuring quality diagnosis and drugs. Default of 24% and failure of 26% were observed. The response was not influenced by resistance pattern or the treatment regimen or duration of treatment prior to MDR-TB.

This study was an attempt to investigate the feasibility of managing MDR TB patients in the field including the diagnosis, drug logistics, ensuring DOT with injection, ensuring compliance and management of adverse reactions. The problems faced included difficulty in initial hospitalisaton, identifying a motivated provider residing closer to the patient who can give injections and motivate the patient to continue 18-months of treatment. In our series less than half the patients were hospitalized or stayed for more than 10 days in the hospital. This was probably due to the fact that the hospital was at least 50km away from their homes and patients were not able to stay away from the work. The prolonged nature of treatment, apart from innumerable visits for drug intake includes periodic visits to the nodal center for clinical and laboratory evaluations. Financial assistance was given when patients attended the nodal centre.

One of the major problems encountered in the field was finding a DOT provider who could give intramuscular injection to the patients. Rural patients received their injections from the village heath worker whenever they were available at the sub-center and on other occasions either from a private provider by paying a fee or from the primary health center. Patients from the urban area either attended TRC outpatient clinic or took treatment from their referral hospital/practitioner. All efforts should be taken before starting treatment to identify a DOT provider nearer to the patient's residence, who could administer injections, possibly by involving net work of private providers available in most villages.

Drugs were supplied from TRC, Chennai as there was no established treatment strategy for MDR-TB patients in the study area at that time. Packing of drugs, transporting to the field, handing it over to the DOT provider and ultimately to the patient required constant supervision and monitoring at every step.

The poor cure rate observed (36%) in the current study, is similar to another report from our centre, where only 31% of 105 patients treated with S/KmEtoZE and 47% of 30 treated with salvage regimen containing OfxH600 and 2-4 drugs from Am/Eto/T/Z were cured[16]. Similarly a study done from Denver in 1993, reported a successful treatment outcome of 56%, despite a median stay for more than 7 months in the hospital. Similarly studies from USA, Argentina, and Peru have reported favourable outcomes of around 45%[2-4]. The unsuccessful response to therapy prescribed in these series was strongly associated with greater number of drugs received previously and male sex[2] and resistance to more than 5 drugs[2-4]. A recent report from India had shown 68% cure among 28 patients who had completed 24 months of treatment schedule[5.] On the other hand, studies done at Korea, Vietnam, Netherlands and Turkey had shown favourable treatment outcome above 75%[6-9]. The reason for good response in the New York group was attributed to the fact that majority (68%) of

their patients had not given history of anti-tuberculosis treatment earlier. In the Korean study response was assessed excluding patients who were discharged prematurely and those who had additional intervention. It was contrary to the current series, where all patients had received varying duration of anti-tuberculosis treatment with 4 or 5 drugs. The poor success rate was observed mainly due to the high default (24%) and failure (26%) rates. The supply of ATT under partial DOTS may also be one of the factors responsible for the poor outcome. Promising results have come from the independent study from Lativa and the combined outcome of 5 DOTS Plus sites showing success rate of 66% and 70% [1,17].

Recently, there have been a number of reports on XDR TB. There is global concern over the emergence of XDR-TB which leaves patient virtually untreatable using currently available anti-TB drugs. WHO and CDC on data from 2000-2004 found that XDR has been identified in all regions of the world but is most frequent in countries of former Soviet Union and in Asia. Four percent of MDR from USA, 19% from Latvia met the criteria of XDR[18]. In our series one patient had XDR TB at the start of treatment. Of 33 MDR TB patients treated with regimens containing Km and Ofx, two had emergence of XDR TB. To our knowledge this is the first report on the existence of XDR TB from India.

Response to treatment could be correctly predicted based on the 6-month smear results in 40 of 42 patients. Thus 6-month smear status can be used as a surrogate marker for response to treatment and those who remain positive at 6-months can be considered for change of treatment.

Implications for the programme

India is currently planning to implement DOTS Plus in two sites. There is a need to ensure reliable DST, prompt and regular delivery of drugs to the PHC, identifying a provider for prolonged DOT who can give injection and who has the social skills to maintain patients on such a prolonged treatment with repeated motivation and ability to management of minor adverse reactions.

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