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Outcome of 66 Patients with Multi-Drug Resistant (MDR) TB Treated with DOTS Plus Regimen: South-East area, Ahmadabad Experience.

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Research Article

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ABSTRACT

To analyze demographic, clinical, radiological and bacteriological profile, drug sensitivity pattern, adverse drug reactions and treatment outcome in MDR TB patients treated with DOTS plus regimen. From August 2007 to March 2010, 66 patients who were on DOTS plus regimen were analyzed retrospectively. Data collection was from treatment cards and medical records. Sputum smear and culture examination for tubercle bacilli were performed every month in intensive phase (IP) started at the end of third month and then every third month in continuation phase (CP) until end of treatment. Serum creatinine was measured every month in IP and quarterly in CP. Regular chest radiography was done at commencement of therapy, at the end of intensive phase and at the end of treatment. Weight was done at regular interval. Clinical assessment made regularly for clinical improvement and tolerance of drugs. All data compiled and meta-analysis was done for outcome profile and various factors leading to adverse outcome. Data were expressed in means ± SD and ranges. Comparison of the success and failure/default/death/treatment completed groups was made using Student's independent samples *t* tests for numeric variables and x^2 test for categoric variables. A p value, 0.05 was considered significant. 25 patients (37.87%) were cured, 4 patients (6.06%) failed, 17 patients (25.75%) defaulted and 17 patients (25.75%) died and 3 patients (4.54%) had completed treatment (TC) of total 66 patients who were put on CAT IV treatment. Mean time for sputum smear and culture conversion were 4.2±2.2 and 4.29±2.5 months, respectively. Extensive lung lesion, cavitations, poor adherence to treatment, high initial bacterial load and BMI less than 18 are variables associated with poor treatment outcome. 40 (60.60%) patients experienced adverse drug reactions and 18 of them required drug modifications. Initial drug sensitivity pattern, sputum smear and culture conversion at end of third and fourth month are not indicators to predict outcome. Sputum smear and culture conversion are very well correlated with clinical and radiological improvement. More emphasis should be given to reduce default and death rate to achieve good cure rate.

INTRODUCTION

The emergence of drug resistant mycobacteria has become a significant public health problem world over creating an obstacle to effective TB control. Drug resistance can develop if basic TB control fails at a variety of different stages: for example, when diagnosis and/or treatment are inaccurate, drug supplies are not consistent or the quality of the medicines is poor or patients are not adherent to their treatment. Confirmed Multi Drug Resistant tuberculosis (MDR TB) case is defined as an MDR-TB suspect who is sputum culture positive and whose TB is due to Mycobacterium tuberculosis that are resistant in-vitro to at least isoniazid (H) and rifampicin (R). (The culture and Drug Sensitivity Test results are being from an RNTCP accredited laboratory). As per the WHO global TB report 2011, estimated number of MDR TB cases out of notified pulmonary TB cases in India is 64000 (range, 44000 to 84000) emerge annually. A WHO report says that nearly 60% of estimated 310,000 cases of MDR TB diagnosed in

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2011, occurred in China, India & Russia. The treatment regimen for MDR-TB is long and costly, placing a strain on both health systems and patients.

In present study we sought to analyze treatment outcome and factors associated with poor outcome.

SUBJECTS AND METHODS

Data collection

Data of 66 patients of MDR were obtained from medical records like treatment card and registers from August 2007 to March 2010.

The details of demographic data, chemotherapy, adverse drug reactions to drugs, regularity of treatment, follow up assessment as well as regular sputum bacteriology and chest radiography results were recorded.

Sputum bacteriology and other investigations

Sputa were collected in sterile Mc cartney bottles containing cetyl pyridinium chloride (CPC) or falcon tubes. All specimens were subjected to culture for mycobacterium tuberculosis and drug susceptibility testing for isoniazide (H), rifampicin (R), ethambutol (E) and streptomycin (S) on Lowenstein Jensen (LJ) medium which were sent in CPC bottle. Specimen collected in falcon tubes were subjected to Line Probe Assay (LPA) to know sensitivity of H and R only. Sputum culture and drug sensitivity results are available after three to four months in LJ media while LPA is a rapid diagnostic test which gives result within few days. Because of this fact RNTCP has adopted LPA method for diagnosis of MDR TB cases after August 2009. However LPA is not useful for follow up sputum cultures hence follow up cultures are being done by LJ media.

Prior to starting treatment all patients were underwent detailed clinical, serological, bacteriological, radiological evaluation. Thyroid, hepatic, renal function tests and complete blood counts were done. HIV testing by enzyme linked immunosorbent assay done after pre test counselling and informed consent. All patients were referred to DOTS plus site where DOTS plus treatment were started after evaluation.

DOTS plus regimen

As per RNTCP guidelines this regimen includes six drugs kanamycin (Km), ethambutol (E), pyrazinamide (Z), cycloserine (Cyc), ethionamide (Eto) and ofloxacin(Ofx)/levofloxacin (Lfx). These drugs to be taken daily except Km which is to be taken six days per week. Intensive phase includes all six drugs and continued for six to nine months depending on culture report while continuation phase includes four drugs (Cyc, Eto, E, ofx/lfx) taken for 18 months. PAS (Para amino salisylic acid) is reserved drug for patients who develops adverse drug reaction or who conceives while on therapy.

Patient monitoring

Patients were regularly assessed for clinical and radiological improvement. Weight done every month, chest radiography was done six monthly and frequent assessments done for adverse events. Sputum smear and culture were done at the end of 3, 4, 5, 6, 7 month and then every 3rd month in continuation phase. Renal function test was done every month in intensive phase and then every 6th month in continuation phase.

Outcome definitions

Cure

An MDR-TB patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.

Death

An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.

Treatment failure

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Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three cultures are positive.

Treatment default

An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.

Treatment completed

Patients who completes the treatment but do not fit in criteria of cure.

Data was compiled and analysed for different parameters like age, gender, socio economic status, co morbid conditions, reason for MDR suspect, method of diagnosis, drug sensitivity pattern to first line anti tuberculosis drugs, adverse drug reactions, sputum smear and culture conversion, weight gain, radiological improvement.

RESULTS

Demographic and clinical profile

Sixty six patients were put on category IV regimen after diagnosis of MDR TB. Mean age was 34±11.54 years (range, 16 to 62 years). Forty three (65.15%) patients were male and 23 (34.85%) were female. Mean body weight was 41.80±10.82 kg (range, 20 to 60 kg). Mean body mass index (BMI) was 18.67 (range, 14 to 23.5). Concomitant medical diseases were present in 23 patients (34.85%). These included hypertension, COPD, hyperlipidemia, chronic alcoholic liver disease. Four (6.06%) patients were immunocompromised, of which one (1.51%) were HIV positive and three (4.54%) were diabetic. HIV positive patient was already known case and on anti-retroviral therapy. In present study no patient was having thyroid abnormality before initiation of treatment. There was not any female with pregnancy before or after initiation of therapy.

Drug sensitivity pattern: MDR TB was diagnosed by either LJ culture or Line Probe Assay (LPA). And drug sensitivity pattern on L J media and LPA depicted in Table 1 and Table 2 respectively.

Table 1: Sensitivity Pattern of Culture on L.J. Media (n= 49; 74.24%)

Resistant to	No. of Patients (n=)	Percent (%)
SHER	31	63.26
SHR	9	18.36
HRE	2	4.28
HR	7	14.28

Table 2: Sensitivity Pattern of LPA (n=17; 23.75%)

Resistant to	No. of Patients (n=)	Percent
HR	13	76.48%
R only	4	23.52%

Adherence to therapy

Forty five (68.18%) patients were regular in therapy. Twenty three (34.84%) had poor adherence to therapy, which was defined as missing more than 20% of the designated number of doses.

Outcome

All the patients who failed therapy were suspected as XDR TB and second line drug sensitivity were sent which revealed non XDR TB (sensitive to ofloxacin) in two and remaining two patients were turned out to be XDR TB cases. Total seventeen patients had defaulted therapy - 4 (23.52%) due to social reason, 8 (47.05%) due to migration to other state or territory and 5(29.4%) due to adverse drug reaction.

Of the variables that might be associated with the adverse treatment outcome are presence of cavitations, BMI< 18, extensive lung lesion, poor adherence to therapy and initial high bacterial load (Table 3).

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Table 3: Demographic, clinical, bacteriologic and treatment characteristics in 66 MDR TB patients with different outcome.

Variable	Treatment outcome		P value
	Success (n=25)	Failure/ death/ default/ Treatment completed (n=41)	
Age	30.44 (mean)	32.51 (mean)	NS
Male sex	13(52%)	30 (73.17%)	NS
Presence of cavity	7 (28%)	29 (70.73%)	<0.5
Extensive disease	8 (32%)	30(73.17%)	<0.5
Initial bacterial load	3+ n=3	3+ n=13	<0.5
	2+ n=10	2+ n=14	NS
	1+/Scanty bacilli n=12	1+/ Scanty bacilli n= 14	NS
Poor adherence	0	16 (39.02%)	HS
HIV positivity	0	1 (2.43%)	NS
Diabetes	2 (8%)	1 (2.43%)	NS
Adverse events which needed drug modifications	6(24%)	12 (29.26%)	NS
BMI ≤ 18	7 (28%)	19(70.37%)	<0.5

NS=Not Significant; HS= Highly Significant

Analysis of expired cases

Study revealed that among total 17 expired patients, one patient expired before 3 month of treatment, 5 patients had completed treatment up to 3-6 months and 11 patients had taken treatment for more than 6 months. Out of these 11 patients who had taken treatment for more than 6 months; 5 patients had culture conversion and 6 patients remained culture positive.13 (76.47%) had far advanced lung lesion on chest radiography, one (7.14%) patient was diabetic. Five (35.71%) patients developed adverse drug reaction which required modifying treatment, of these one patient developed severe jaundice, altered behaviour and joint pain. 11 patients had BMI ≤ 18.

Adverse drug reactions

Of 66 patients, 40 (60.60%) had adverse drug reactions of varying severity. The most common ones were related to central nervous system. Modification of drug regimen required in 18 patients. Nine of them required to terminate cycloserine treatment after a mean of 4.1± 3.2 months (range, 1 to 9 months) because of depression (n=3), altered behaviour (n=3), suicidal attempt (n=1), insomnia (n=1) and seizure (n=1). Two patients required termination of aminoglycosides after a mean of 2.5± 2.1 months (range 1 to 6 months) because of nephrotoxicity or otovestibular toxicity. Four patients had severe joint pain and so needed to discontinue pyrazinamide. Ethionamide was stopped in three patients due to development of jaundice (n=1), hypothyroidism (n=1) and severe gastritis (n=1). Various adverse drug reactions observed during therapy are depicted in table 4.

Table 4: Adverse Drug Reactions Observed.

System	Manifestations	No of patients (%)	Actions taken for ADR
Gastro intestinal	Nausea, vomiting, epigastric discomfort	7(10.60%)	Symptomatic treatment. Ethionamide stopped (n=1)
Central nervous	Insomnia, depression, seizure, suicidal attempt, polyneuropathy	14(21.2%)	Cycloserine stopped in 9 patients
Skeletal	Joint pain	8 (12.12%)	Symptomatic treatment (n=4); Pyrazinamide stopped, para amino salicylic acid added (n=4)
Otovestibular	Giddiness, tinnitus, impaired hearing	3 (4.54%)	Kanamycin stopped (n=2)
Hepatobiliary	Jaundice	1(1.51%)	Pyrazinamide and ethionamide stopped temporarily
Endocrinal	hypothyroidism	1(1.51%)	Ethionamide stopped.
Renal	Renal function impairment	1 (1.51%)	Kanamycin stopped temporarily
Dematologic	Hypersensitivity, rashes	1(1.58%)	Symptomatic

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DISCUSSION

In our study younger population with lower weight patients are more affected in contrast to other studies [1,2,3] while other demographic profile and clinical characteristics were similar to other studies, with male patients' predominance.

Among the variables that were found to be independently associated with adverse outcome of patients, the presence of cavitations might affect drug penetration and thus decrease the efficacy of anti-tubercular drugs. It was found that cavitary lesion per se, irrespective of drug sensitivity pattern was associated with poor treatment outcome [4]. Irregularity of treatment linked with adverse outcome is not unexpected and emphasizes that importance of directly observed therapy in the management of tuberculosis, which should be mandatory for all patients with MDR TB [5]. In our study major cause of irregularity was migration to other territory and alcoholism which is also observed in other study [6]. In a developing country like India malnutrition is a major health problem and very important factor which leads to poor immunity and so associated with adverse outcome as indicated by low BMI (less than 18), which is comparable to one study (unpublished data, DOTS plus pilot project, Gujarat). Similar results were observed in one another study also [7].

Second line anti tubercular treatment adverse events leading to treatment interruption or defaultation was observed in present study. Most common adverse event was related to gastro intestinal which is also seen in other studies [7,8,9,10]. Central nervous system related adverse events were second most common which lead to omission of cycloserin in our study.

In this cohort study of MDR TB patients, those who responded achieved sputum culture negativity during early months of therapy, usually within four months. This concurs with a study of HIV negative subjects with MDR TB. In our study sputum culture conversion at three to four month was not predictive of eventual cure, which was shown in other series [11].

The poor cure rate (37.87%) was observed in the current study, is similar to another report from tuberculosis research centre, where only 36% cure rate was observed [10]. Similarly study carried out from Denver in 1993, reported success rate of 56%. Similarly studies from Argentina, Peru and USA have reported positive treatment outcome of around 45% [1,12,13]. The unfavorable outcome shown in these series was strongly associated with greater number of drugs received previously and male sex and resistance to more than five drugs. A report from India had shown 68% cure rate [14]. On the contrary to our study other reports from Vietnam, Korea, Netherland and Turkey had shown cure rate of above 75%. [3, 15,16,17] In present study poor cure rate was observed mainly due to high default (25.75%) and death rate (25.75%). Regimens for treatment of MDR tuberculosis are very long (≥20 months), poorly tolerated, expensive, and substantially less effective than first-line treatment of drug-susceptible tuberculosis [18]. WHO reports show that only 48% of the more than 25 000 patients with MDR tuberculosis from 107 countries who started MDR tuberculosis treatment in 2009 completed their treatment successfully because of deaths (15%), treatment interruptions (14%), treatment failure (9%), and insufficient data (14%) [20]. An individual meta-analysis of 9153 patients with MDR tuberculosis from 32 observational cohorts reported similarly dismal findings (success 54%, default 23%, failure or relapse 8%, and death 15%) [20]. Patients with strains of tuberculosis that had acquired additional resistance to second-line injectable drugs, to fluoroquinolones, or both (XDR tuberculosis) [21] had poor outcomes. Health system failures generally underpin the emergence of drug resistance in a population. Factors such as poor diagnostic facilities, insufficient regulation of access to antibiotics, poor implementation of the directly observed treatment short-course programme, and lack of tuberculosis drugs lead to monotherapy and intermittent treatment. In India, huge variations in the quality of management practices in public-sector and private-sector facilities probably play a major part in the emergence of drug-resistant tuberculosis [22]. The highest burden of drug resistance arises in countries that can afford first-line drugs, but have weak health-care systems that are likely to generate MDR and XDR tuberculosis [19]. This situation explains the relative over-representation in Brazil, Russia, India, China, and the emerging economies in the Asia-Pacific region.

SUMMARY

This study describes meta-analysis of patients on DOTS plus regimen. Migration to other region or territory, alcoholism and drug toxicity are important factors leading to defaultation or poor treatment adherence and ultimately low cure rate in MDR TB treatment. All patients should be explained and counseled at multiple level regularly to improve adherence to therapy. Low BMI is indicator of poor health status and associated with high mortality so more emphasis should be given to improve nutritional status of all these patients. Emergence and spread of MDR TB can threaten the global TB control. The treatment of MDR TB is prolonged, expensive and often unsuccessful. Hence prevention of MDR TB is more important rather than treatment. Strengthening the program by intensely evaluating treatment regimens, assuring treatment adherence, supporting true DOTS, aggressive and proactive management of adverse events and infection control are very essential.

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