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Treatment outcome of multi-drug resistant tuberculosis in a tertiary care hospital in Karachi

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Abstract

Objective: To assess the outcomes of pulmonary multidrug-resistant tuberculosis (MDR-TB) patients treated at Ojha Institute of Chest Diseases (OICD), a reference hospital for TB in Karachi, Pakistan.

Methods: Clinical study for the period 1996-2006, with follow-up until June 2007 was performed. All the culture and sensitivity proven cases of MDR pulmonary TB were initially admitted for 3-6 months till the sputum converted negative. Treatment regimen was decided on individual basis, and included 4-6 drugs. Supervised treatment was given to all patients during the hospitalization. After discharge from the hospital, patients were followed at monthly interval at the outpatient department of OICD for 18 months total.

Results: Five hundred and seventy nine adult patients (59.93% male) with mean age of 32.44 ± 12.63 years were studied. All patients had a history of treatment with first line anti-tuberculosis drugs. Treatment was successful in 227 (39.2%). The mortality rate was 27(4.6%) during hospitalization. During admission 83(14.3%) left treatment and 239 (41.2%) were lost to follow-up during treatment. Treatment failure was observed in three patients.

Conclusion: The treatment success rate in this study is satisfactory but high default rate is a challenge in the management of MDR tuberculosis (JPMA 59:694; 2009).

Introduction

Multi-drug resistant tuberculosis (MDR-TB) is an increasing health problem in Pakistan. According to World Health Organization (WHO),[1] the estimated cases of MDR tuberculosis in Pakistan are 3.4% and 36% in new and previously treated cases of tuberculosis respectively. Globally, Pakistan is ranked 8th in terms of estimated number of tuberculosis (TB) cases, with an incidence of 181/100,000 persons.

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The treatment of MDR tuberculosis is difficult because it is expensive, prolonged and complicated which in turn result in poorer outcome.[2] There is no reported data from Pakistan on treatment outcome of MDR tuberculosis.

We are presenting our experience in treating a large series of patients with MDR pulmonary tuberculosis.

Patients and Methods

This observational study was done at Ojha Institute of Chest Diseases (OICD) from 1996 to 2006. The Ethical review committee of OICD approved the study. OICD is a 350-bedded postgraduate institute with five chest clinics in Karachi. It registers 4500-5000 TB patients annually and provides them treatment using DOTS (Directly Observed Treatment Short course) strategy. The Institute is the pioneer in providing treatment for MDR TB patients since 1996.

We reviewed the records of 579 culture proven admitted cases of MDR pulmonary tuberculosis patients registered from 1996 to 2006. Susceptibility testing and drugs that had not been used in the past guided therapy. We administered minimum four drugs (range 4 to 7 drugs; median 5 drugs) during the intensive phase including one injectable aminoglycoside (mostly Kanamycin) and Quinolone (Ofloxacin in most of the patients) from the 2nd line and also included the sensitive drug if any from the first line according to the sensitivity results on individual basis. During the continuation phase we used 3 to 4 oral drugs according to the sensitivity from the first and 2nd line drugs. The dosages used are mentioned in Table-1.

Table-1: Second line anti-tuberculosis drugs with dosage.

Drug	Dose
Kanamycin	15mg/Kg/day im (single dose)
Ethionamide	15 mg/Kg/day (Single or two divided doses)
Cycloserine	15 mg/Kg/day (Single or two divided doses)
PAS	120 mg/Kg/day (Two divided doses)
Ofloxacin	15 mg/Kg/day (Single or two divided doses)
Thiacetazone	150 mg/day (Single dose)

During hospitalization the sputum for AFB (Acid Fast Bacilli) smear were done monthly. AFB cultures were done every three months. Patients remained in the hospital until the sputum smear became negative. Supervised treatment was given to all patients during hospitalization. Every possible effort was made to continue therapy in patients who developed adverse drug reactions. Appropriate measures were taken to combat side effects.

After a period of initial hospitalization, patients were discharged with one month of medications and advised to report to MDR clinic within one month. They were followed in outpatient clinic monthly. Drugs for one month were pre-packed and handed over to the patient. The patients were evaluated for clinical, microbiological and radiological response regularly. They were also evaluated for side effects of the medications. Patients were followed by sputum microscopy (three specimens) every three-months and treatment continued for a total of eighteen months. At the end of treatment, patients were asked for follow up at 3, 6 and 12 months or any other time if they developed respiratory symptoms suggestive of tuberculosis that did not resolve in three weeks with treatment or referred from their general practitioner.

The MDR TB treatment outcome definitions were used as follows:

Successful outcome: Patient who completed treatment and consistently had negative smear (Performed every three months in continuation phase).

Treatment default: Patients who did not receive treatment for $\geq$ 2 consecutive months were defined as having defaulted treatment.

Treatment failure: Patients whose smear was positive at the end of six month or whose $\geq$ 2 smears were positive during final 12 months.

Death: Patients who died due to any cause during treatment.

LAMA (left against medical advice): Patients who left hospital against medical advice during initial hospitalization phase.

The definition of successful treatment in this study not in line with the WHO recommended definition which recommends culture results as gold standard.[3] The limitation was non-availability of large-scale culture facility.

SPSS version 14 was used to analyze the data. The results are presented as mean with standard deviation.

Results

A total of five hundred and seventy-nine patients with MDR pulmonary Tuberculosis were registered. Three hundred and forty seven (59.93%) were male and 347 (40.07%) were female; their mean age was 32.44 $\pm$ 12.63 (range 15-78 years). Twelve percent of the patients had unilateral disease while remaining had bilateral extensive fibrocavitary disease. In all patients there was history of multiple courses of ATT intake including the full course of category 2 regimen. The comprehensive detail of previous treatment was not available in most of the patients.

On initial sensitivity report 326 (56.5%) of patients were resistant to all 5 first line drugs. The median number of drugs received was 5 (range 4 to 7). The median duration of hospital stay was 3.8 months. The total duration of treatment was 18 months.

Response to Treatment:

Successful outcome was seen in two hundred and

Table-2: Treatment outcome analysis based on regimen.

Regimen/No of patients	Successful outcome	Default	LAMA	Death	Treatment Failure
KEthOfCtz/49	14 (28.5%)	19 (38.7%)	12 (24.4%)	03 (6.1%)	Nil
KEthOfCtzC /53	23 (43.39%)	16 (30.1%)	10 (1.88%)	04 (7.54%)	Nil
KEthOfCtzC /09	04 (44.44%)	03 (33.33%)	Nil	02 (22.22%)	Nil
KEthOfCP/70	35 (50%)	31 (44.28%)	01 (1.42%)	03 (4.28%)	Nil
KEthOfP /62	15 (24.19%)	42 (67.74%)	01 (1.61%)	04 (6.45%)	Nil
KEthEZOf/101	43 (42.57%)	24 (23.76%)	29 (28.71%)	05 (4.95%)	01 (0.99%)
KOfEthZP/15	08 (53.33%)	06 (40%)	Nil	01 (6.66%)	Nil
KEthCtzOfP/27	12 (44.44%)	13 (48.14%)	01 (3.70%)	01 (3.70%)	Nil
Others/193	73 (37.82%)	84 (43.52%)	29 (15.02%)	05 (2.59%)	02 (1.03%)
Total	227	238	83	28	03

K: Kanamycin, Eth: Ethionamide, Ofl: Ofloxacin, C: Cycloserine, P: ParaAminosalicylic Acid, E: Ethambutol, Z: Pyrazinamide, Ctz: Combination of INH (Isonicotinic acid hydrazide) and Thiacetazone, Others: Regimen not fitting in any of the above, LAMA: leave against medical advice.

Table-3: Discontinuation of ATT due to adverse effects.

Drug	No. Discontinued/total received (%)	Reason for discontinuation (no. of patients)
Cycloserine	16/194 (8.24%)	Homicidal attempt (1), Psychosis, aggressive behaviour, suicide attempt (1)
Kanamycin	07/623(1.12%)	Deafness
Ethionamide	01/497 (0.20%)	Severe vomiting
PAS	04/249 (1.60%)	Hypothyroidism with goiter, Hepatitis
Thiacetazone	3/252 (1.19%)	Abdominal pain

twenty seven patients i.e. 227/579 (39.20%). Eighty-three patients (14.33%) left hospital against medical advice (LAMA) during initial hospitalization, 239 (41.27%) defaulted after discharge, 27 (04.66%) expired due to tuberculosis, while three patients (0.51%) remained positive at the end of one year. Attempts were made to contact patients by phone. However, either their phone number was incorrect or the patient deliberately did not attend the call. Due to non-availability of physical facilities for follow up of defaulted patients, the defaulters could not be traced. All patients (except three) i.e. 466/579 (80.48%) were smear negative at the time of discharge from hospital.

Microbiological Response to Treatment:

Most of the patients 416/579 (71.84%) converted to smear negative at three month, 111 (19.17%) at 04 months while 49 patients (08.46%) took up to six months to convert. Three patients were smear positive at the end of one year so they were labeled as treatment failure.

In Table-2 detailed outcome analysis of different regimens is given. The most successful regimens in patients resistant to all five first line drugs were kanamycin, ethionamide, ofloxacin, cycloserine and para-aminosalicylic acid (KEthOfCP) and kanamycin, ethionamide, ofloxacin, pyrazinamide and para-aminosalicylic acid (KEthOfZP) with 50% & 53% successful outcome respectively. In the first group, total number of patients was small. "Other" regimen consisted of multiple regimens of first and second line drugs according to individualized initial culture report.

Two hundred and thirty nine patients defaulted in the study. They defaulted during the follow up period. Fifty-three patients (21.33%) defaulted within two to three months of discharge, 108 patients (45.18%) defaulted during month 7-12 (Of treatment) while 80 patients (33.47%) defaulted during month 13-18.

Side effects:

During hospital stay, eighty-eight patients (15.19%) developed side effects due to medications. They were managed accordingly but in thirty-one patients (5.35%) one or more antituberculosis drug was discontinued (Table-3). Among the minor side effects the most common were Gastro-intestinal upset i.e. bloating, abdominal pain, nausea, vomiting and diarrhoea. Besides dizziness, anorexia, joint pain, headache and depression was also seen.

The follow up at three and six month had records of only 119 (52.42%) and 48 (21.14%) and all were smear negative.

Relapse Rate:

During the study period, eight patients (03.52%) reported with positive sputum among those who successfully completed the treatment. The gap between completion of treatment and relapse was between months 2 to 8.

Discussion

This is the first largest study from Pakistan on treatment outcome of MDR TB patients. The treatment success rate in this study was 39.2% (227/579). Lockman[4] reported cure rate (defined as "Completed >6 months of therapy and had a negative AFB smear result at end of treatment") of 37% (17/46) which is compatible to our study. Marie et al[5] from France reported 33.33% success rate in their 51 cases. Goble et al[6] had an overall response rate of 56 percent after excluding default and death, but if the overall response of the total patient number is calculated then the rate becomes 87/171 (50.87%). Other authors have also reported low success rate[7-10] varying from 44-51.2% in which full cohort was reported. Our results are not comparable to these studies because of the difference in the treatment success definition. Cultures are more sensitive than smear results and it is quite possible that our results of treatment success would have been lower if we had used the criteria of culture in follow up.

The other observation in this study was a high default rate. Out of 579 patients, a total of 322 (55.6%) defaulted including both during hospitalization and afterward. Lockman et al[4] from Estonia reported high default rate in both of their MDR and drug susceptible groups i.e. 16/46 (35%) and 19/46 (41%) respectively. Other authors have also reported high default rates of 39%[11] and 28.9%[7] from Korea, 29.1%[8] from Taiwan and15.38%[12] from India. We believe that the reason for default/discontinuation of therapy in our setting is

improvement in symptoms as evidenced by high default rate in the latter half. The possibilities of discontinuation due to side effects, long distance to collect medicine, natural disasters like floods cannot be ruled out. To combat these issues we suggest: Intense motivation of patients at the time of registration and discharge, telephonic access to the medical officer for issues arising when patient is at home. Beside after discharge Directly Observed Therapy (DOT) is the most important single measure in decreasing the default and in completing the therapy. In this regard liaison with TB control programme through their DOTS treatment centers will help. Incentives in the form of cash or promotion in service will motivate the staff for this additional work. If any patient defaults, it will be possible to trace and rectify the issues responsible for the default. Besides training of doctors and paramedics in the management of TB generally and MDR TB specifically is essential.

We considered the correlation between past treatment history and response to current treatment but in Pakistan most of the General Practitioners prescribe Anti-tuberculosis treatment (ATT) on radiological ground, without sputum examination. Patients consult another doctor in case symptoms do not improve or side effects are encountered. In some cases they consult a third doctor on recommendation of some friend or family member. Most of the patients do not keep the record. End result is either same drug in different dose or sometime addition of one more drug which in turn results in more resistance.

It has been reported[13] that patients who receive initial therapy in a hospital had significantly higher treatment completion rates (79%) than those treated as outpatients alone (48%, $p < 0.001$). Our treatment completion rate was low in spite of all patients being admitted in the initial phase.

It is recommended[13] that early surgical intervention (e.g., within 6 months after intensive chemotherapy) could be beneficial, even if the patient has a positive result of smear or culture. None of our patient underwent surgery due to non-availability of proper surgical facility otherwise results would have been better as studies[14-16] have shown good results when chemotherapy was combined with surgery.

The relapse rate is quite low in this study. This could be because if the patient who benefitted from the treatment center would report to the same center, once symptoms recurred. The possibility of death has to be considered. It is possible that the patients did not develop a relapse or did not report due to the long distance and financial reasons.

The limitation of this study was that the patients were followed up with sputum smear only as the facility for AFB culture on a large scale was not available. It was therefore presumed, that any patient excreting bacilli was positive or became positive if he/she was excreting viable bacilli. The doubling time of Mycobacterium tuberculosis is 16-24 hours[17] and for sputum to be positive on smear, the bacillary count should be 10,000 bacilli/ml of sputum.[18] Others[19] claim that with optimal laboratory conditions, smear can be positive with only 100-1000 bacilli/ml. If one hundred bacilli are present in the lung then after one month the count will increase to >10,000 and at next examination smear will become positive. The other limitation was lack of follow up after completion of treatment. In resource-limited countries, where default during treatment is high, it is difficult to expect a regular follow up after completion of treatment.

Conclusion

This is the first large study on MDR TB treatment outcome from Pakistan, a high TB burden developing country. The treatment success rate in this study is low and not comparable to other large studies due to the use of smear results rather than the culture in follow up period. Although the initial microbiological response to the treatment was excellent but defaulting from treatment is a major challenge in the treatment of MDR TB in our cohort of patients. Strategies are needed to reduce default rate in this group of patients.

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