Management of Drug Resistant Tuberculosis in a teaching hospital before and after implementation of Programmatic Management of Drug Resistant Tuberculosis

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AB SM AJ conceived idea, AB AJ AN MAK planned the study, AB SM AG drafted the manuscript, SM MAK UU collected data, SM MAK did statical analysis and interpretation, AB ZU ZI MYK AJ critical reviewed manuscript, all the authors approved the final version to be published.

Declaration of conflicting interests

The Authors declares that there is no conflict of interest.

ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is a potential threat to global tuberculosis control. Its management is recommended by WHO in a tertiary care hospital setting with a dedicated team with linkages with TB control programme in the community.

Methods and Methodology: Drug Resistant TB patients were managed at LRH even before this from 1st October 2008 till the launch of PMDT on February 2012. Data during these times were saved in hard as well as in soft. For study purposes all data were converted into SPSS and analyzed the data for percentage and differences by using chi square testing. A P-value of 0.05 was considered to be statistically significant.

Objective: In this study the outcome of patients of cohort of "Pre-PMDT" from Oct 2008 to Dec 2011 is compared with cohort of "Post-PMDT" implementation from 2012 till Dec 2014.

Results: From 2008 to 2014, 956 MDR-TB patients were included in this study. The patients were classified into two cohorts: Pre- PMDT cohort of Non GLC patients (n = 285) and Post- PMDT cohort of GLC patients (n = 671). Statistically significant difference was found in the treatment outcomes of pre and post PMDT. Successful treatment outcome were found to be statistically significant with Post PMDT cohort patients (p = .000) while unsuccessful treatment outcome with Pre PMDT cohort patients (p =.020). Most of the Post-PMDT patients 487 (72.58%) were cured as compared to Pre-PMDT cohort 14 (5%) and found statistically significant (p = .000). Default rate was found to be high in Pre-PMDT cohort 49 (17.2%) as compared to Post-PMDT cohort 5 (0.71%) and statistically significant (p = .000). Failed 1 (0.35%), died 67 (23.50%), transfer out 20 (7%) in Pre- PMDT cohort and failed 36 (5.37%), died 118 (17.59%), transfer out 8 (1.19%) in Post- PMDT.

Conclusion: The study shows significant improvement in treatment outcome of Post PMDT cohort as far as Default rate is concerned.

Key words: DOTS Plus; PMDT; LRH; Khyber Pakhtunkwa; Pakistan

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Introduction

TB resistant strains resistant to INH and Rifampacin called Multi Drug Resistant TB (MDR-TB), is a potential threat to global tuberculosis control.[1] It accounts for 5% of all TB cases globally. The treatment of patients with MDR- and XDR-TB is more complex, toxic and costly and less effective than treatment for other forms of TB. Treatment of MDR TB is challenging and complex and

treatment success is considerable less than drug susceptible TB. Its management is recommended by WHO in a tertiary care hospital, with a dedicated team with linkages in TB control program in the community.[2]

Pakistan is one of the top listed countries ranking fifth among the top 22 high burden countries. MDR-TB among new cases is 4.2%, and in retreatment cases 16% and on the basis of this rate WHO has estimated an annual incidence of about 15000 MDR-TB cases in Pakistan.[3]

In Pakistan, National TB control program (NTP) is working with a mission "A TB FREE PAKISTAN". The NTP target is to enhance the capacity of public and private sectors to detect and manage 80% of the estimated smear positive MDR-TB incident cases by year 2015. [4]

The increasing rate of MDR and XDR-TB in Pakistan underscores the importance of effective treatment programs of drug-resistant TB. NTP Pakistan started Programmatic management of MDR-TB from 2009 in selective tertiary care centre of some cities of the country. Before the launch of PMDT in Pakistan some of the centre in Pakistan was already managing MDR-TB from their own resources. Lady Reading Hospital (LRH) Peshawar was one among such centres.

Having to learn from the experience of first pilot project of Oct 2005,[4-6,10] hospital started managing MDR-TB in more organized way as second project from October 2008 but PMDT was then formally launched in LRH in 2012. So LRH had 2 cohort, Pre PMDT (LRH supported) cohort from Oct 2008 to Dec 2011 and Post PMDT (NTP supported) cohort from Jan 2102 to onward.[4-6]

The rational of this study is to assess the treatment outcome of MDR-TB before and after implementation of programmatic management of drug resistant TB (PMDT) in Lady Reading hospital (LRH).

Methodology

Settings: Drug resistant TB unit, Department Pulmonoloy, Lady Reading hospital, which was provincial reference point for the management of MDR-TB in Khyber Pakhtunkhwa province.

Study Design: This study was a retrospective review of all patients treated for MDR-TB by the Chest Unit, Lady Reading Hospital Peshawar, Pakistan from October 2008 to December 2014 and compared Pre-PMDT cohort with Post PMDT cohort.

Duration: As this is comparative study and consists of two cohorts, one before the start of PMDT and other after the initiation of PMDT. Pre-PMDT consists of patients who were initialized their treatment between 2008 and 2012 and Post-PMDT included those patients who were enrolled for treatment after 2012. In Post-PMDT cohort we have selected two years data and consists of those patients who have completed their treatment and their final outcomes be declared.

Sampling Method and Sampling Size: Consecutive sampling was done to collect data on community mechanisms of treatment supervision. Sample size comprised 956 patients.

Treatment Regimens and Protocol: To be included for treatment, patients required culture and drug susceptibility testing (DST). The initial diagnosis of TB was made either by Rifampacin resistance on TB gene Expert, positive sputum smear and/or AFB culture.

For study under review, patients were grouped in two cohorts. Pre-MDT cohort of LRH consisted of high risk for MDR-TB patients enrolled from October 2008 till Dec 2011, after enrollment, their data was recorded on a proforma in excel form specially designed by LRH team for recording and follow up. Each patient had his treatment supporter allocated. Each patient was advised to come for monthly follow up. Patients were only provided free medicine and free sputum microscopy arranged by the unit from various sources like Pakistan chest society, Provincial TB control Programme (PTP) and LRH administration. Other facilities like follow up sputum cultures, social support, conveyance allowance, psychologist services, home visits and routine investigations, according to guidelines were not provided due to shortage of resources.

After February 2012 when Memorandum of Understanding (MoU) was signed between NTP, LRH and Association for Community Development (ACD) DR-TB patients were registered as Post-PMDT cohort/NTP supported where all the above mentioned facilities were given to the patients. Resource person were recruited by NTP, and recording and reporting was monitored on ENRS, psychological services, social support and home visits were given special attention to address any problems with default or late follow up. Social support in the form of Food basket and convince allowance was not only given to the patients but also the treatment supporter accompanying the patient responsible for giving DOTS.

Treatment regimen in both cohort were same except that drugs in Pre-PMDT cohort was from local market while in Post-PMDT cohort, drugs were from global fund. Treatment for MDR-TB was started with Kanamycin, levofloxacin, Ethionamide, PAS, Vita 6 for 8 to 12 months intensive phase and Ofloxacin,

Ehtionamide, PAS and Vita 6 for 16 months continuation phase.

Additional information in the computerized database included age, sex, weight, chest radiograph findings at initiation of treatment, sputum smear results, sputum cultures, all medications and their dosages, and outcome. Outcomes were declared cure, treatment completed, treatment failure, loss to follow-up and death.

Laboratory testing: Sputum smear microscopy was done in microscopy laboratory in chest OPD- LRH and Cultures were processed at Agha Khan University Hospital, Deptt. Of Microbiology Karachi, using the direct proportion method with dilutions of culture inoculated onto Löwenstein-Jensen (LJ) media. DST against INH, RMP, PZA, EMB, ofloxacin (OFX), cycloserine (CS), ethionamide (ETH), and streptomycin (SM). DST against PZA was recognized to be unreliable. Careful attention was paid to the pH of LJ media for PZA testing (pH 5.5).

In Pre-PMDT cohort AFB culture was done at base line and at six months interval due to patient bearing themselves the cost of DST from AKU, while sputum smear was done monthly free of cost to patients.

In Post-PMDT, DST was done at base line and then AFB culture was done monthly in intensive phase and then bimonthly in continuation phase while sputum smear was done monthly.

Data Collection and analysis: Data collection tools included:

1. Compilation sheet bearing indicators in relation to treatment outcome.
2. ENRS

Statistical Analysis: All data were analyzed using the SPSS software (15.0 version). Comparisons of categorical variables were performed using the Pearson Chi-square test to compare different groups. All variables with a P value, 0.20 in the univariate analysis were included in the multivariate logistic regression model. A P value of 0.05 was considered to be statistically significant.

Results

From 2008 to 2014, 956 MDR-TB patients were taken for this study. The patients were classified into two cohorts: Pre- PMDT cohort of Non GLC patients (n = 285) and Post- PMDT cohort of GLC patients (n = 671). Pre –PMDT cohort consisted of patients registered from Oct 2008 till Dec 2011, while Post MDT cohort were from Jan 2012 till Dec 2014.

Table 1: Baseline characteristics of study cases

Patients characteristics	**No. of patients (%) N =**		**Total**
Demographic	Pre PMDT	Post PMDT	N= 956(%)
Gender	N= 285(%)	N= 671 (%)	
Male Female	126 (44.21) 159 (55.79)	292 (43.52) 379 (56.48)	418(43.72) 538 (56.28)
Age (Years)			
< 35 years ≥ 35 years	193(67.71) 92 (32.28)	461(68.70) 210 (31.30)	654 (68.41) 302 (31.59
Weight (Kg)			
≤ 40 kg ≥ 41 kg	____ ____	258 (38.45) 413(61.55)	____ ____
Registration group			
New Previously treated after failure Previously treated after Relapse Previously treated after loss to follow up Other	5 (1.75) 209(73.33) 6 (2.11) 6 (2.11) 59 (20.70)	65 (9.69) 327 (48.73) 88 (13.11) 13 (1.94) 178 (26.53)	70 (7.32) 536 (56.07) 94 (9.83) 19 (1.99) 237(24.79)
Previous TB treatment			
Yes No	280 (98.24) 5 (1.75)	606 (90.31) 65 (9.69)	886 (92.68) 70 (7.32)
Previous use of second-line drug			
Yes No	126 (44.21) 158 (55.44)	72 (10.73) 599 (89.27)	198 (20.71) 757 (79.18)

The below table shows percentage of the demographic characteristics Pre-PMDT cohort patients treated in (2008 to 2011) Non GLC patients and Post-PMDT cohort (2011 to 2014) GLC patients at this center. The table shows that 418 (43.72%) of the patients were male and 538 (56.28%) were female. Male patients of Pre-PMDT cohort was 126 (44.21%) and female patients were 159 (55.79%). Male patients of Post-PMDT cohort was 292 (43.52%) and 379 (56.48%) was female. It also shows that most of the patient's age 654 (68.41%) was less than 35 years. And registration group of most of the patients 536 (56.07%) were previously treated after failure of TB treatment. Previously used second-line drugs by patients are 126 (44.21%) in Pre-PMDT cohort and 72 (10.73%) in Post-PMDT cohort. (Table 1)

Total number of patients is 956, including 285 patients of Pre-PMDT cohort and 671 of Post-PMDT cohort. Of these 285 patients in Pre-PMDT cohort (LRH supported) non GLC, 14 (5%) were cured, 134 (47%) were labeled as treatment completed, 67 (23.50%) died, 49 (17.0%) defaulted, 1 (0.35%) failed and 20 (7.00%) patients were transferred out (Table. 2, Fig. 1), whereas in PMDT cohort total number of patients registered so far is 671 GLC patitents. Among these patients 7 (1.04%) are still under treatment, 487 (72.58%) cured, 9 (1.34%) completed, 36 (5.37%) failed, 05 (0.71%) defaulted, 118 (17.59%) died, 8 (1.19%) transferred. (Table 2)

The above table shows the comparison of treatment outcomes of Pre-PMDT and Post-PMDT cohort by regression analysis. Statistically significant difference was found in the treatment outcomes of pre and post PMDT. Successful treatment outcome were found to be statistically significant with Post PMDT cohort patients (p = .000) while unsuccessful treatment outcome with Pre PMDT cohort patients (p =.020). Most of the Post-PMDT patients 487 (72.58%) were cured as compared to Pre-PMDT cohort 14 (5%) and found statistically significant (p = .000). Last to follow up rate was found to be high in Pre-PMDT cohort 49 (17.2%) as compared to Post-PMDT cohort 5 (0.71%) and statistically significant (p = .000). Failed 1 (0.35%), died 67 (23.50%), transfer out 20 (7%) in Pre- PMDT cohort and failed 36 (5.37%), died 118 (17.59%), transfer out 8 (1.19%) in Post- PMDT.

Table 2: Comparison of Treatments Outcomes of Pre-PMDT and Post PMDT Cohort

Treatment Outcome	Pre- PMDT N= 285	Post- PMDT N = 671	Total N = 956
Still on Rx	0	7 (1.04%)	7 (0.73%)
Cured	14(5%)	487 (72.58%)	441 (46.13%)
Completed	134(47%)	9 (1.34%)	140 (14.64%)
Failed	1 (0.35%)	36 (5.37%)	29 (3.03)
Defaulted	49 (17.2)	5 (0.71%)	50 (5.23)
Died	67 (23.50%)	118 (17.59%)	180 (18.83)
Transfer out	20 (7.00%)	8 (1.19%)	28 (2.93%)

Table 3: Comparison of Treatment Outcomes by regression analysis of Pre-PMDT and Post PMDT Cohort

Treatment Outcome		Pre- PMDT N= 285	Post- PMDT N = 671	p-value	p-value
	Still on Rx	0 (0%)	7 (1.04%)	0.102	
Successful treatment outcome	Cured	14 (5%)	487 (72.58%)	0.000	.000
	Completed	134 (47%)	9 (1.34%)	0.000	
Unsuccessful Treatment outcome	Failed	1 (0.35%)	36 (5.37%)	0.056	.020
	Defaulted	49 (17.2)	5 (0.71%)	0.010	
	Died	67 (23.50%)	118 (17.59%)	0.042	
	Transfer out	20 (7.00%)	8 (1.19%)	0.033	

Discussion

This is, to our knowledge, the first study on MDR-TB treatment outcomes in a teaching hospital comparing two cohort pre and post PMDT in the same centre with different human resource/programme settings. The

wide difference of sample size in Pre PMDT cohort of 285 patients versus 671 in post PMDT is self explanatory could be explained by the fact that because at that time LRH was working independently on the basis of MDR diagnosed /referred from their own OPD in limited resources' with no formal liaison with other DHOs or TB centers and LRH team had taken the initiative on their own to manage MDR-TB on the best possible resources made available to them at that time, while Post PMDT cohort consisted of patients from Global fund approved project, which was launched with formal trainings of not only in LRH but also DHOS and TB centers had trainings and Gene expert machines were installed and referrals to LRH site were made mandatory as it was the only PMDT centre of KPK.

We observed a significantly higher proportion of successful treatment in patients being treated after 2011 than before 2011. While the pre PMDT cohort of patients treated for MDR-TB in LRH are also promising keeping in view of their limited resources with the proportion of successfully treated patients compared to that seen in GLC approved DOTS PLUS projects post-PMDT cohort.

Our study of two cohorts of MDR-TB patients shows encouraging results in terms of cure rates, especially considering high rates of previously treated after the failure of anti-TB drugs, with less than 35 years of patient age and previous second-line treatment in these cohorts. Over all treatment success rate were found to be high 496 (73.91%) in post-PMDT cohort as compared to pre-PMDT cohort 48% which is comparable to the results seen previously in some studies.[7-9]

This outcome has shown improvement over the first experience of MDR-TB in KPK 1993 to 1998 in where cured/treatment complete were 54%, treatment failure 10 %, died 2% and default 34%.[10]

Similar high treatment success rates were also observed, in a recent study carried out in Heilongjiang province of China, the initial treatment success rates were 88.5% (100/113) and 73.4% (94/128) for newly diagnosed and retreated MDR-TB cases respectively[7,11] and 68.4 % achieved treatment success, 22.8% were lost to follow up, 3% were transferred out and 1.8% died.[12] As compared to our study successful outcome was seen in 496 (73.91%) in post PMDT cohort. MDR-TB treatment programs with largely HIV negative patients have reported cure rates and death rates of 61–77% respectively.[13,14] However, this figure is relatively lower in comparison to cure rates of about 60% observed in Denver, New York and Netherlands, to over 80% seen in South Korea, Turkey, Hong Kong and Peru.[9]

Failure rate is 1 (0.35%), Died 67 (23.50%), transfer out 20 (7%) in pre pmdt cohort as compared to post pmdt Failure rate is 36 (5.37%), Died 118 (17.59%), transfer out 8 (1.19%).

The proportion of defaulters among MDR-TB patients in pre pmdt (49 (17.2%) and post pmdt (5 (0.71%) patients in our study were close to that observed in Beijing (92/528, 17.4%)[7] and Uzbekistan (12/87, 14% for MDR-TB).[15] A higher proportion of defaulters were observed in a few other studies such as in South Africa (144/491, 29.0% for MDR-TB)[16] and South Korea (453/1407, 32.0% for MDR-TB).[17]

Default rate was found to be high in Pre-PMDT cohort 49 (17.2%) as compared to Post-PMDT cohort 5 (0.71%). Moreover, default appears to be a global phenomenon, with rates over 15% in several countries, including Korea (32%),[18] Taiwan (29%),[19] Russia (20%),[20] Italy (17%),[21] Argentina (20%)[22] and Peru (19%).[23]

The death rate in our Pre-PMDT and Post PMDT cohort was 67(23.50%) and 118 (17%) respectively. These values are on a high side and need to be reduced. The death mainly occur to patients who were diagnosed late and due to the MDR-TB patients conditions were debilitated and caused other problems which caused there death. However the observation noted that died (23.50%) were slightly more as compared to Post-PMDT 17 %, and it is statistically significant. (p=.042) it raises question on the toxic effect/regimen of global fund drugs in post PMDT group.

The statistically significant difference of cured in Post-PMDT Cohort versus Pre-PMDT cohort was due to the fact that follow up Sputum Culture could not be done on regular basis in Pre-PMDT cohort due to the cost being paid by patients themselves, hence they were declared treatment completed on the basis of regular sputum smear negative. This factor has led to statistically significant difference of treatment completed in Pre-PMDT cohort as compared to Post-PMDT cohort.

The improved treatment outcomes in post PMDT could be attributed to the fact that there had been no established standard guidelines for treating TB patients in the hospital until 2008, when the National Tuberculosis Programme (NTP) treatment guidelines were widely adopted in Pakistan. The improved treatment outcomes could also be linked to the overall success in TB control achieved in PMDT throughout the country due to increased government commitment and more intensive TB control measures such as covering the WHO Directly Observed Therapy Short-Course (DOTS) strategy nationwide, strengthening

local public health facilities and national infrastructure and providing man power.

Conclusion

Post MDT had better outcome in terms of default rate due to strong commitment of NTP and close liaison of DR-TB physician, HDL resource person, DTO and MDR-TB patients. Interms of success rate Pre-PMDT also had good outcome despite limited resource which again shows that a dedicated team is also important while managing MDR-TB patients .

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