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Original Article

Treatment Results of Multidrug-Resistant Tuberculosis Patients in the Aegean Region

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Abstract

OBJECTIVE: We aimed to evaluate 109 rifampicin-resistant or multidrug-resistant tuberculosis patients who are treated in Izmir Chest Diseases MDR Tuberculosis Centre.

MATERIAL AND METHODS: The patient profile, side effects, treatment success, and mortality of rifampicin-resistant or multidrug-resistant tuberculosis patients who were followed up and treated in our hospital's tuberculosis service between 2010 and 2018 were analyzed retrospectively.

RESULTS: Of the rifampicin-resistant or multidrug-resistant tuberculosis patients, 83 (76.1%) were male and the mean age was 46.3 ± 16.3 years. Of the cases 13 (11.9%) had rifampicin resistance without isoniazid. Since 5 out of 109 patients diagnosed with multidrug-resistant tuberculosis emigrated to other countries, the treatment results of 104 patients were evaluated. As a result of the treatment, the cure was achieved in 81 (77.9%) patients and treatment was completed in 13 (12.5%). Treatment success was found as 90.4%. No patient experienced recurrence. The mortality rate was determined as 9.6%. The cure rate of patients treated with ≥6 drugs (90.9%) was statistically significantly ($P = .029$) higher than the group treated with ≤5 drugs (71.8%).

CONCLUSIONS: Multidrug-resistant tuberculosis treatment is a long-term, financially burdensome practice that may cause serious side effects and complications, and it requires strict discipline. The fight against tuberculosis can be successful with tuberculosis control programs that are pursued with determination.

KEYWORDS: Tuberculosis, treatment, mortality, multidrug-resistant tuberculosis

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a globally important public health problem. Rifampicin-resistant (RR) and MDR-TB strains are more difficult to treat than drug-susceptible tuberculosis (TB) and threaten global progress toward End-TB Strategy targets.[1] Multidrug-resistant tuberculosis is multifactorial. It feeds on mistakes made in treatment and difficulties in drug supply.[2] In addition, the coronavirus disease 2019 (COVID-19) pandemic has adversely affected the fight against TB.[3-5]

Multidrug-resistant tuberculosis is resistant to both isoniazid (INH) and rifampicin. There may also be other drug resistance together. Rifampicin is the most important drug in the treatment of TB; once resistance develops, treatment of patients with TB becomes difficult. Rifampicin-resistant/multidrug-resistant tuberculosis requires treatment with second-line drugs.[6] In the treatment of MDR-TB, less effective drugs are used when compared to the treatment of drug-susceptible TB. It is more toxic, long-lasting, and expensive. Success rates are lower.[7,8]

Therefore, with this study, we aimed to evaluate the demographic, clinical data, resistance rates, and treatment results of RR/MDR-TB patients diagnosed and followed up in our hospital.

MATERIALS AND METHODS

Patient Data

Rifampicin-resistant/multidrug-resistant tuberculosis patients diagnosed and treated in the Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital between 2010 and 2018 were analyzed retrospectively in terms of demographic, clinical, side effects, treatment success, and mortality. Informed consent for clinical treatment was obtained from all patients taken to the study. For this study, 22/07/2020 dated approval was obtained from the Ethics Committee of the Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital with the number 16. Data from the patients were analyzed through hospital archive records.

Chest x-rays and, if available, thorax computed tomography of the cases recorded in the hospital imaging system were examined. The radiological extent was evaluated under 2 groups as one-lung and two-lung involvement.

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Microbiological Data

For each sample, acid-resistance staining with standard fluorochrome and/or Kinyoun method, culture on BACTEC 960 (MGIT) (Becton Dickinson, Sparks, Md, USA) system, and Löwenstein–Jensen medium were performed. The susceptibility test of patient samples was performed using the BACTEC 960 (MGIT) system in accordance with the manufacturer's recommendations. Drug resistance in new cases was defined as drug resistance observed in patients who had not used TB drugs before or had used them for less than a month. In treated cases, drug resistance was defined as resistance to a drug that the patient had previously used for more than 1 month.[9,10]

Treatment and Follow-Up Data

The drugs were classified according to the recommendations of the World Health Organization (WHO) and the National Tuberculosis Guidelines, which were up-to-date in the time period (between 2010 and 2018) of the patients we included in the study.[11] At least 5 active drugs, 1 parenteral and 1 quinolone, were included in the treatment regimen of the MDR-TB patient. Drugs that were sensitive in the drug sensitivity test but had never been used before were regarded as active drugs, whereas drugs that had been used in the past yet were sensitive in the test were seen as suspicious drugs. Drugs that were resistant and that had previously been used were both accepted as inactive. While creating the treatment regimen of the MDR-TB patient, the drugs were added step by step from the first group to the fifth group.

Grouping Antituberculosis Agents

Group 1

First-line oral agents: Isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb)

Group 2

Injectable agents: Kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)

Group 3

Fluoroquinolones: Moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)

Group 4

Oral bacteriostatic second-line agents: Ethionamide (Eto); protionamide Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)

Group 5

Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients): Clofazimine (Cfz); linezolid (Lzd); amoxi cilli n/cla vulan ate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); clarithromycin (Clr).

MAIN POINTS

- In the treatment of multidrug-resistant tuberculosis, less effective drugs are used when compared to the treatment of drug-susceptible tuberculosis. It is more toxic, long-lasting, and expensive. Success rates are lower.
- High treatment success rates are possible in patients with rifampicin-resistant or multidrug-resistant tuberculosis treated under direct observation.
- The fight against multidrug-resistant tuberculosis should be continued with determination without compromising the foreseen program, despite all obstacles, including the coronavirus disease 2019 pandemic era.

For MDR-TB, a regimen consisting of at least 5 active drugs from 5 groups of drugs was applied according to the guideline recommendation. In this treatment, amikacin, capreomycin, moxifloxacin, ofloxacin, linezolid, cycloserine, prothionamide, para-aminosalicylic acid, and thioacetazone were used by choosing according to susceptibility and side effects. For the MDR-TB treatment initiation period, a regimen consisting of at least 5 drugs and parenteral drugs was used for at least 6 months until sputum smear and cultures were consistently negative. Drugs were given regularly by a directly observed treatment (DOT) program. For the treatment of 13 RR-TB patients, the regimen using first-option drugs recommended in the same guideline was applied. In addition, special treatment consisting of first-option drugs was administered to 8 MDR-TB patients who did not accept the second-option drug treatment specified in the guideline. Amikacin was preferred as the parenteral drug in the second-option drug treatment, and capreomycin was used according to culture in 2 patients. Moxifloxacin was preferred as quinolone. Ofloxacin was used in 11 patients. The treatment was administered under direct observation. The treatment period was applied for 24 months after the culture became negative. The updated WHO 2020 guidelines recommend an all-oral bedaquiline (Bdq)-based shorter regimen in place of the previously recommended injectable-based shorter regimen, with one of the key eligibility criteria being that patients are not resistant to the fluoroquinolones. The shorter regimen comprises (6 Bdq plus 4-6 Lfx/Mfx-Cfz-Eto-)-Hh-E-Z/5 Lfx/Mfx-Cfz-E-Z. The WHO 2020 guidelines also recommend a 6- to 9-month regimen that comprises a new medicine, pretomanid, together with Bdq and linezolid (i.e., the BPaL regimen) for the treatment of MDR-TB with additional resistance to fluoroquinolones; however, this regimen is to be used under operational research conditions only. However, in the time period during which our study was undergoing, Bdq-based shorter regimen was not reached because there were no resources available for this course of treatment.[12]

For the sputum conversion period, the date of the first negativity was used when the smear and cultures of 2 groups of sputum taken at least 30 days apart were negative. In patients who completed treatment without evidence of treatment failure criteria, 3 or more consecutive negative cultures that were taken at least 30 days apart after the baseline period were defined as cure. Patients who completed the treatment without any signs of failure but did not show 3 or more consecutive negative cultures that were taken at least 30 days apart after the initial period were considered to be treatment completion. The sum of the cases with cure and treatment completion was taken as treatment success.

Statistical Analysis

Statistically descriptive analyses were performed with Statistical Package for the Social Sciences software version 25.5 software (IBM Corp.; Armonk, NY, USA). Results were presented as median (min-max), number and percentage (%). Shapiro–Wilk and Kolmogorov–Smirnov tests of

normality were used to determine whether the parameters used in the comparison of the groups were normally distributed. Mann–Whitney U-test and Student's *t*-test were used to compare continuous variables, and chi-square and Fisher's exact tests were used to compare categorical data. Results were presented as median (min-max), mean ± SD, and number and percentage (%). $P < .05$ was considered statistically significant.

RESULTS

In our center, 109 patients were diagnosed with RR/MDR-TB. The mean age of 109 patients was determined as 46.3 ± 16.3 (17-81). Of 109 patients, 83 (76.1%) were male and 26 (23.9%) were female. Eight patients (7.3%) were foreign nationals (Table 1). Human immunodeficiency virus (HIV) was positive in 2 patients (1.8%). Of 109 (2.7%) patients, 3 had extrapulmonary TB. These were 1 pleurisy, 1 skin, and 1 lymphadenitis TB patient. In the radiological appearance of the lesions, involvement was detected in 1 lung in 26 patients (23.9%) and in 2 lungs in 83 patients (76.1%) (Table 2). There was additional disease in 33 (30.3%) patients. The most common comorbidities were diabetes mellitus 15.6%, cardiovascular 5.5%, and chronic renal failure 4.6%. Of 109 patients, 13 (11.9%) had RFM resistance not accompanied by INH. Amikacin resistance was studied in 71 (65.1%) patients, and resistance was detected in 8 (11.2%) patients. Moxifloxacin resistance was studied in 65 patients (59.6%), and resistance was found in 3 (4.6%) patients. Linezolid resistance was studied in 57 patients (52.2%), and resistance was detected in 2 (3.5%) patients. Pyrazinamide resistance was studied in 77 (70.6%) patients, and resistance was detected in 29 (37.6%) patients. Two patients had resistance to 9 drugs, and 8 patients had resistance to 8 drugs.

Table 1. Demographic Properties

	Patients (n = 109)
Properties	**n (%)**
Age, years, mean ± SD (min-max)	46.3 ± 16.3 (17.0-81.0)
Sex	
Female	26 (23.9)
Male	83 (76.1)
Educational status	
Illiterate	1 (0.9)
Primary education	47 (43.1)
High school	59 (54.2)
University	2 (1.8)
Marital status	
Married	79 (72.5)
Single	30 (27.5)
Profession	
Unemployed	36 (33.0)
Employed	53 (48.6)
Retired	20 (18.3)

Table 2. Clinical Properties

	Patients (n = 109)
Properties	**n (%)**
Smoking history	
Never smoked	26 (23.9)
Active smoker	69 (63.3)
Quit	14 (12.8)
Family history of MDR-TB	4 (3.7)
Comorbidity	
Diabetes mellitus	17 (15.6)
Cardiovascular	6 (5.5)
Chronic renal impairment	5 (4.6)
Malignancy	4 (3.6)
COPD	3 (2.7)
Chronic liver disease	1 (0.9)
Schizophrenia	1 (0.9)
Silicosis	1 (0.9)
Resistance history	
Drug resistance in new cases	46 (42.2)
Drug resistance in treated cases	63 (57.8)
Radiological involvement	
Single lung	26 (23.9)
Bilateral	83 (76.1)

COPD, chronic obstructive pulmonary disease; MDR-TB, multidrug-resistant tuberculosis.

Treatment

Since 5 out of 109 patients diagnosed with RR/MDR-TB emigrated to other countries, the treatment results of 104 patients were evaluated. The mean time between admission to the hospital and initiation of the treatment was 26.7 ± 30.4 (1.0-120.0) days (Table 3). The mean duration of the treatment initiation period was 5.8 ± 2.5 (1.0-14.0) months. The mean culture conversion time was 2.3 ± 1.6 (1.0-12.0) months. The duration of hospitalization was 6.4 ± 6.2 (0.0-36.0) months. The total treatment time was 21.1 ± 6.6 (8.0-30.0) months. Drug side effects were

Table 3. Treatment Characteristics

Duration (days) between admission and treatment initiation, mean ± SD (min-max)	26.7 ± 30.4 (1.0-120.0)
Initial period durations (months), mean ± SD (min-max)	5.8 ± 2.5 (1.0-14.0)
Culture conversion (months), mean ± SD (min-max)	2.3 ± 1.6 (1.0-12.0)
Duration of hospitalization (months), mean ± SD (min-max)	6.4 ± 6.2 (0.0-36.0)
Total treatment duration (months), mean ± SD (min-max)	21.1 ± 6.6 (8.0-30.0)
Patients underwent surgery	0 (0.0)

Table 4. Drug Side Effect

	Patients (n = 104)
	n (%)
No side effect	44 (42.3)
Side effect present	60 (57.7)
Hepatotoxicity	20 (19.2)
Ototoxicity	18 (17.3)
Psychiatric disorder	13 (12.5)
Hypothyroidism	12 (11.5)
Visual impairment	11 (10.6)
Nephrotoxicity	7 (6.7)
Hematological disorder	5 (4.8)
Neurotoxicity	4 (3.8)
Allergic reactions	2 (1.9)

observed in 60 patients (57.7%). The most common side effects were hepatotoxicity 19.2% and ototoxicity 17.3%. In 29 (27.9%) patients who experienced side effects, the drug was withdrawn from the treatment regimen (Table 4). No patient underwent surgical treatment.

As a result of the treatment, cure was achieved in 81 (77.9%) patients and treatment was completed in 13 (12.5%) (Table 5). Treatment success was found to be 94 (90.4%). All patients were followed up starting from the end of the treatment within the study period. No recurrence was detected in any patient. Ten patients (9.6%) died. Eight of the deaths were due to TB and 2 were due to non-tuberculous causes (malignancy, ruptured aortic aneurysm). The data were evaluated in terms of factors affecting the treatment outcome. Seventy-one (68.3%) patients treated with 5 or fewer drugs and 33 (31.7%) patients treated with 6 or more drugs were compared. The cure rate (90.9%) of the patients treated with 6 or more drugs was found to be higher than the other group (71.8%). This value was statistically significant ($P = .029$).

DISCUSSION

Treatment for multidrug-resistant tuberculosis is more expensive, carries a higher risk of adverse effects, and lasts longer than therapy for drug-susceptible TB. Therefore, it is the cause of increased mortality and morbidity and the treatment success rate is lower. However, successful treatments are possible with disciplined practices. In our study, there was no case with treatment failure or out of follow-up; 77.9% cure, 12.5% treatment completion rate was achieved, and

Table 5. Treatment Outcome

	Patients (n = 104)
	n (%)
Cured	81 (77.9)
Treatment completed	13 (12.5)
Treatment success	94 (90.4)
Treatment failed	0 (0.0)
Died	10 (9.6)
Recurrence	0 (0.0)

treatment success is 90.4%. No recurrence was detected during the 9-year follow-up. In one of the different RR/MDR-TB studies conducted in different centers, in the study of Törün et al.[13] 77.6% treatment success was reported. Karagöz et al[14] reported a cure rate of 86.4%, Arpağ et al[15] reported a cure rate of 84.4%, and Ünsal et al[16] reported a cure rate of 53.1% in their studies. The treatment success rate of RR/MDR-TB was reported as 57% in the World Health Organization Global Tuberculosis 2020 Report.[6] Brode et al[17] found treatment success as 83.9%. Singh et al[18] reported a 74.5% cure. The treatment success of our center is similar to or even higher than many other centers. Compared to the results of other studies, we attribute this high success rate to treatment with long-term hospitalization and treatment under direct observation.

In our study, the mortality rate was 9.6%. Karagöz et al[14] reported a mortality rate of 7.8%, Ünsal et al[16] reported a mortality rate of 3.7%, and Arpağ et al[15] reported a mortality rate of 7.8%. Singh et al[18] found a mortality rate of 10.2% in the study, and Xu et al[19] found a mortality rate of 8.6%. The results of the study were found to be similar to other studies. In addition, HIV positivity is one of the reasons that increase mortality in RR/MDR-TB patients. There was no HIV infection in 104 patients whom we gave the result of treatment, so a comparison could not be performed. After diagnosis, 5 patients for whom we did not present treatment results left to complete their treatment in their country or region (not evaluated case) and 2 of these patients were HIV-positive. In the study population, HIV-positive RR/MDR-TB comorbidity was observed in 2 foreign patients. Therefore, no data could be presented in our study on HIV infection and RR/MDR-TB comorbidity mortality.

In the radiology of our patients, 76.1% had involvement in both lungs. Karagöz et al[14] reported the rate of involvement in both lungs as 61.2% and Singh et al[18] as 94.9%. The fact

Table 6. Treatment Outcomes of Patients Treated in Accordance with the Drug Regime

	Cured Completed (n)	Treatment Follow-Up (n)	Lost to (n)	Died (n)
	n (%)	n (%)	n (%)	n (%)
First-line drugs (n = 21)	11 (52.3)	9 (42.8)	-	1 (4.7)
Second-line drugs (≤5 drugs) (n = 50)	40 (80.0)	3 (6.0)	-	7 (14.0)
Second-line drugs (≥6 drugs) (n = 33)	30 (90.9)	1 (3.0)	-	2 (6.0)

that most of the patients had extensive disease is a finding consistent with the literature.

Mean sputum conversion (culture conversion) was found as 2.3 ± 1.6 months. Arpağ et al[15] reported the mean sputum conversion 1.9 ± 1.03 months. Li et al[20] found an average of 85 days for sputum conversion (culture conversion) in 359 MDR-TB patients. As it is seen, our culture conversion rates are similar to other literature results.

The mean duration of hospitalization was 6.4 ± 6.2 months. Arpağ et al[15] reported the mean duration of hospitalization as 162.7 days and stated that long-term hospitalization increases the chance of treatment success. Olaru et al[21] reported the mean duration of hospitalization as 128 days. In our study, the mean total treatment duration was found as 21.6 ± 6.6 months. In the study by Olaru et al,[21] this period was reported as 19.5 months on average. The length of the hospitalization is higher in our study compared to other studies; we think that a longer duration of hospitalization increases the chance of DOT and increases the rate of coping with complications and side effects. We believe that the long duration of hospitalization has an effect on our high treatment success rates. Although the length of duration of hospitalization may have increased the cost, there is a need for studies on this subject.

Side effects were observed in 57.7% of the cases in this study. The most common side effect was hepatotoxicity with 19.2%. Ototoxicity was observed with a rate of 17.3%, and psychiatric disorders with a rate of 12.5%. The drug was withdrawn from the regimen in 27.9% of the cases. Törün et al[13] evaluated 263 MDR-TB cases in terms of side effects and found side effects at a rate of 69%, and the most common side effect was ototoxicity at a rate of 41.8%. Treatment changes were performed in 55% of patients who experienced adverse effects. Karagöz et al[14] found side effects at a ratio of 37.9%, Ünsal et al[16] 60.9%, and Arpağ et al[15] 45.5%. In a meta-analysis by Wu et al[22] in which 5346 MDR-TB patients were evaluated in terms of side effects, 57.3% of the patients were found to have experienced at least 1 side effect. The 3 most common adverse events were gastrointestinal disorders at a rate of 32.1%, ototoxicity at a rate of 14.6%, and psychiatric disorders at a rate of 13.2%. They found that MDR-TB treatment should be changed in 70.4% of the patients who developed side effects. Also in our study, side effects were observed in 1 of every 2 patients. Surgical treatment may be helpful in addition to medical treatment in the treatment of MDR-TB. In our study, no patient underwent surgical treatment. Karagöz et al[14] did not find a statistically significant difference between the groups with and without treatment success in terms of adjunctive surgical treatment. There are studies reporting that surgical resection increases the chance of treatment success.[23-25]

Although Karagöz et al[14] did not find a significant ratio between the number of drugs and treatment success in their study, an average of 5.3 ± 0.8 drugs were used in the treatment of MDR-TB in our study. The cure rate of patients who used 6 or more drugs in the treatment was found to be higher than the patients who used 5 drugs or less, and it was found to be statistically significant. (P = .029). Patients who used 6 or more drugs stayed at the hospital longer, but similar side effects and death rates were observed. We believe that these treatment regimens should be given a chance in patients who can tolerate 6 or more drugs, although they have achieved acceptable success rates with 5 drugs (Tables 6 and 7).

Table 7. Comparison of Treatment Characteristics According to Drug Groups in MDR-TB Patients

	Treatment with ≤5 Drugs	Treatment with ≥6 Drugs	
	n = 71	n = 33	
	n (%)	n (%)	*P*
Total duration of treatment (months) median (min-max)	18.0 (1.0-29.0)	25 (11.0-30.0)	.001
Duration of hospitalization (months) median (min-max)	4.0 (0.0-23.0)	8.0 (0.5-36.0)	.002
Side effect	37 (52.1)	23 (69.7)	.091
Cure	51 (71.8)	30 (90.9)	.029[+]
Treatment completion	12 (16.9)	1 (3.0)	.047
Treatment success	63 (88.7)	31 (93.9)	.402
Died rate	8 (11.3)	2 (6.1)	.402

MDR-TB, multidrug-resistant tuberculosis.
[+]Statistically significant.

In our study, 13 RR-TB and 8 MDR-TB patients were treated with first-line drugs. This is because in the national TB guideline recommendations between the years 2010 and 2018 when our study was conducted, first-line drugs were recommended to RR-TB patients. Eight MDR-TB patients are patients treated in the first years of this period, and major treatment was started until the results of resistance appear. Resistance tests were completed in 1 or 2 months. The first-line pharmacological therapy that the patients received during this time period was successful from a clinical, radiological, and laboratory aspect, and they refused the second-line therapy. Therefore, they completed their treatment with first-line drugs. Treatment success was achieved in these patients, and no recurrence was detected. There are other studies in the literature that applied major treatment in MDR-TB patients in the same years.[26,27] However, in the following years, as a result of the more frequent use of molecular rapid resistance tests in our hospital, the recommendations of the WHO and the new national TB guideline[9] and literature data, the diagnosis of RR/MDR-TB was made faster and second-line treatment was applied to each RR/MDR-TB patient.

CONCLUSION

Our study results showed that high treatment success rates are possible in patients with RR/MDR-TB treated under direct observation. The fight against TB is an important public health war. We believe that the fight against MDR-TB should be continued with determination without compromising the foreseen program, despite all obstacles, including the COVID-19 pandemic era.

Ethics Committee Approval: The study was approved by the medical ethics committee of the Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital with the number 16.

Informed Consent: Informed consent for clinical treatment was obtained from all patients taken to the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflict of interest to declare.

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