ORIGINAL ARTICLE

Treatment effectiveness and outcome in patients with a relapse and newly diagnosed multidrug-resistant pulmonary tuberculosis

Dmytro Butov[1], Valeriy Myasoedov[1], Mykola Gumeniuk[2], Galyna Gumeniuk[2], Oleksandra Choporova[1], Anton Tkachenko[3], Oleksandra Akymenko[4], Olena Borysova[1], Olena Goptsii[5], Yevhenii Vorobiov[6], Tetiana Butova[6]

[1]Department of Phthisiology and Pulmonology, Kharkiv National Medical University, Kharkiv; [2] Department of Technologies of Treatment of Nonspecific Lung Diseases, National Institute of Phthisiology and Pulmonology named after FG Yanovskyi NAMS of Ukraine, Kyiv; [3]Department of Biochemistry, Kharkiv National Medical University, Kharkiv; [4]Medical Division #3, Regional Anti-TB Dispensary #1, Kharkiv; [5]Department of Internal Medicine #1, Kharkiv National Medical University, Kharkiv; [6]Department of Internal Medicine, VN Karazin Kharkiv National University, Kharkiv; Ukraine

ABSTRACT

Aim To investigate the treatment effectiveness and outcome in patients with pulmonary tuberculosis relapse and newly diagnosed multidrug resistant pulmonary tuberculosis (MDR-TB).

Methods A total of 240 pulmonary MDR-TB patients, including 114 ones with tuberculosis relapse and 126 cases of newly diagnosed pulmonary tuberculosis, were examined. Effectiveness of the basic antimycobacterial therapy course was evaluated based on the time to normalization of tuberculosis clinical manifestation, sputum culture and acid-fast bacilli stain conversion, cavity closure, disappearance of infiltrative and focal changes in the pulmonary tissue. Treatment outcomes were evaluated as cured, treatment completed, treatment failed, died and lost to follow-up according to the World Health Organization guidelines.

Results When assessing the treatment effectiveness in patients with MDR-TB, a worse clinical and chest radiograph dynamics was observed in tuberculosis relapse against the background of high parameters of treatment failure (18.4 %) and low cured (34.2 %) compared with newly diagnosed pulmonary tuberculosis (7.1% and 58.7 %, respectively) ($p=0.008$ and $p<0.001$, respectively).

Conclusion Standard treatment effectiveness in patients with newly diagnosed MDR-TB manifested by faster improvement and stabilization of health, earlier sputum culture and smear conversion, higher frequency of cavity closure and achievement of certain clinical and radiographic improvement against the background of fewer cases of treatment failure and a higher number of cured patients compared with MDR-TB relapse.

Key words: *Mycobacterium,* X-ray, culture, microscopy

Corresponding author:
Dmytro Butov
Departments of Phthisiology and Pulmonology, Kharkiv National Medical University
Nauky Avenue 4, 61022, Kharkiv, Ukraine
Phone: +38095 015 90 58;
E-mail: dddimad@gmail.com
ORCID ID: https://orcid.org/0000-0002-8792-901X

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INTRODUCTION

Tuberculosis is a leading cause of poor health and one of the most common causes of death worldwide. Furthermore, tuberculosis accounts for numerous deaths from HIV/AIDS (1). The emergence of tuberculosis forms that are resistant to anti-tuberculosis drugs is a huge challenge to the End TB strategy of the World Health Organization (WHO), which aims at reducing tuberculosis incidence by 90% and decreasing tuberculosis mortality by 20% by 2035 compared to 2015 (2). Thus, resistant forms of tuberculosis, in particular multidrug-resistant tuberculosis (MDR-TB), are a global threat to humanity. MDR-TB is defined as a tuberculosis in which *M. tuberculosis* (MTB) is resistant to rifampicin and isoniazid, which are the most effective drugs for tuberculosis treatment in accordance with the history of their administration in 127 countries (3,4). Moreover, chemoresistant tuberculosis more frequently develops especially in patients with tuberculosis relapse than among those with newly diagnosed pulmonary tuberculosis (5,6). It is worth noting that the issue of tuberculosis recurrence remains of huge practical importance nowadays, since the incidence of tuberculosis reactivation in patients who suffered from active tuberculosis has remained high for decades (7). Thus, high rates of resistant tuberculosis may be observed due to an increase in the incidence of cases with tuberculosis relapse (8).

To succeed in reducing the prevalence of chemo resistant tuberculosis, it is necessary to understand the complexity of tuberculosis treatment and evaluation of its outcome (8). Proper understanding and resolution of the issue of tuberculosis relapse could prevent the spread and increase in the amount of tuberculosis patients, especially those with chemo resistant forms, by restricting the major type of tuberculosis transmission, namely the airborne spread of *M. tuberculosis*.

We have decided to conduct this study, since the prevalence of relapse MDR-TB has been increasing for years in the world. Furthermore, in our clinical practice, clinical features of relapse tuberculosis form have drawn attention compared to newly diagnosed pulmonary tuberculosis. Understanding of treatment effectiveness and outcomes may provide novel insights into the prevention of relapses exactly for this cohort of patients.

Thus, the aim of this research was to investigate the effectiveness and outcomes of treatment in patients with tuberculosis relapse and newly diagnosed pulmonary MDR-TB.

PATIENTS AND METHODS

Patients and study design

A retrospective observational cohort study was performed on registry data obtained from the Regional Anti-tuberculosis Dispensary #1, Kharkiv, Ukraine. A total of 240 patients with pulmonary MDR-TB, including 114 cases of tuberculosis relapse (group 1) and 126 patients with newly diagnosed pulmonary tuberculosis (group 2) aged between 20 years and 70 years, were enrolled. The period of inclusion lasted from 2012 to 2017.

The randomization allowed providing equal distribution of baseline characteristics, namely age, gender, height, and body weight (Table 1).

To be eligible for participation in this study, patients must have met the following inclusion criteria: male or female sex, age of 18 to 60 years, multi-drug resistant pulmonary tuberculosis, tuberculosis relapse, newly diagnosed pulmonary tuberculosis, full completion of the inpatient phase of care. Exclusion criteria included pregnancy, lactation, tuberculosis relapse two or more times, incomplete in-patient phase of care, groups with the compromised immunological status (HIV, diabetes mellitus, malnutrition, patients receiving immunosuppressive therapy, including cytostatic, corticosteroid, radiation therapy and TNF-α, and other conditions that comply with WHO guidelines) (9).

Active pulmonary tuberculosis was defined in accordance with the medical history and clinical findings, which were compatible with tuberculosis, chest X-ray examination demonstrating lung involvement, and smear positivity for acid-fast bacilli, as well as positive cultures for MTB.

The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University, Kharkiv, Ukraine).

Methods

Upon hospitalization to the anti-tuberculosis dispensary, isoniazid, rifampicin, pyrazinamide, and ethambutol were prescribed to patients assuming that the causative agent was suscepti-

ble to these drugs. Mutations in an *rpoB* MTB gene were determined using Xpert MTB/RIF (10) within several days to confirm the diagnosis of rifampicin-resistant tuberculosis (RR-TB). Then, the standard chemotherapy was administered: pyrazinamide, prothionamide (ethionamide), second-line injectable drugs, fluoroquinolone, cycloserine, and p-aminosalicylic acid. This treatment lasted until the outcome of bacteriological resistance tests was obtained. Treatment was prescribed based on the MTB susceptibly profile on the basis of the outcome of MTB resistance culture tests. Doses of anti-tuberculosis drugs were selected with respect to the body weight. A treatment of MDR-TB included two phases: intensive (administration of drug injections during at least 8 months) and continuation (administration of injectable forms was cancelled). The latter lasted for at least 12 months.

Effectiveness of the basic course of anti-tuberculosis chemotherapy was evaluated according to the following parameters: the time to normalization of tuberculosis clinical manifestations, smear conversion, cavity closure, disappearance of infiltrative and focal changes in the lung tissue, as well as total clinical treatment effectiveness (8).

Time to normalization of the most important tuberculosis clinical manifestations and conventional diagnostic methods under the influence of standard chemotherapy was evaluated by the disappearance of intoxication and chest-related symptoms. Discontinuation of the intoxication syndrome was confirmed by the presence of subjective signs (increased appetite, disappearance of general weakness, fatigue, sweating) in patients, normalization of body temperature and body weight, and changes in urinalysis and other signs, which were considered symptoms of tuberculosis. Disappearance or reduction of shortness of breath, cough, chest pain, haemoptysis, and pulmonary haemorrhages was also assessed.

The treatment outcome was assessed according to the WHO guidelines: cured, treatment completed, treatment failed, died, and lost to follow-up (11).

Standard microbiological examinations of a sputum smear stained in accordance with Ziehl–Neelsen, and culture Lowenstein–Jensen methods (12) were performed prior to the enrolment of patients. Furthermore, they were conducted monthly starting from the beginning of the treatment. Isolates of MTB were tested for susceptibility to the first- and second-line anti-tuberculosis drugs using commercially available kits (Tulip Diagnostics Pvt Ltd., Goa, India). Similarly, liquid cultures (Mycobacterial Growth Indicator Tube – MGIT-960, Becton Dickinson, Franklin Lakes, NJ, USA) were used for diagnostic purposes. *M. tuberculosis* resistance to the first-line anti-tuberculosis drugs was determined when reagents were available.

Sputum culture was carried out for all patients. Sputum smear microscopy was not performed in four and five patients in the group 1 and group 2, respectively, because of sputum missing. In these cases, bronchoalveolar lavage fluid (BALF) was performed instead.

The bacterial load was evaluated by a Ziehl–Neelsen method: smear-negative (acid-fast bacillus were not found in 100 fields), smear single positive (+) (10-99 acid-fast bacillus per 100 fields), smear double positive (++) (1-9 acid-fast bacillus per fields), smear triple positive (+++) (over 10 acid-fast bacillus in each fields) (8,12).

The bacterial load was assessed at a Lowenstein–Jensen medium also: solitary colonies of sputum/BALF MTB: single positive (1+) (20-100 colonies), double positive (2+) (100-200 colonies), triple positive (3+) (200-500 colonies - almost totally covered), quadruple positive (4+) (over 500 colonies - totally covered) (8,12).

Pathological features, i.e. the severity of the disease and changes in the localization of the process in lungs, were evaluated by X-ray examination.

Monitoring was performed at the beginning of the treatment every 4 months during the intensive phase, and every 6 months at the continuation phase.

Statistical analysis

Standard parametric Student's t-test (13) was chosen based on the outcomes of Shapiro-Wilk and Kolmogorov-Smirnov normality tests. The difference was considered to be statistically significant at $p<0.05$.

RESULTS

A total of 240 patients with pulmonary MDR-TB, including 114 cases of tuberculosis relapse (group 1) and 126 patients with newly diagnosed

pulmonary tuberculosis (group 2) were included. There was no statistically significant difference among the groups relating to the age, gender, height and weight (Table 1).

Table 1. Baseline characteristics of patients with pulmonary tuberculosis

Characteristic	Group 1 (n = 114)	Group 2 (n = 126)	p
Mean age (±) (years)	41.9±1.2	43.8±1.1	0.256
Gender (No, %)			
Male	87 (76.3)	100 (79.4)	0.563
Female	27 (23.7)	26 (20.6)	
Height (cm)	171.6±0.8	172.2±0.8	0.620
Weight (kg)	63.1±1.1	62.8±1.1	0.891

Group 1, pulmonary tuberculosis relapse; Group 2, newly diagnosed pulmonary tuberculosis

An analysis of 114 patients with tuberculosis relapse revealed that among patients with newly diagnosed pulmonary tuberculosis 37 (32.4%) were diagnosed until 2014, while 77 (67.6%) after 2014.

Post-treatment changes in cardinal symptoms

Upon admission to the hospital intoxication syndrome was observed in 96 (out of 114; 84.2%) patients with TB relapse and in 83 (out of 126; 65.9%) patients in the group 2 (p=0.001). During the intensive phase of chemotherapy, we observed an earlier stoppage of intoxication syndrome in the patients of group 2 than in the patients with relapse of tuberculosis (Table 2). After the first month of the treatment, there were still 51 (61.4%) and 78 (81.2%) patients who had intoxication syndrome in the patients with newly diagnosed pulmonary tuberculosis and in the group with relapse, respectively (p=0.003).

After four months of the treatment, intoxication was almost completely eliminated in 44 (out of remaining 51 after the first month of the treatment; 86.3%) patients in the group with newly diagnosed pulmonary tuberculosis and 38 (out of 78; 48.7%) patients with relapse (p<0.001). After eight months of chemotherapy, intoxication ceased in one (out of remaining seven after four months of the treatment; 14.3%) and 24 (out of 40; 60.0%) patients with relapse (p=0.030) (Table 2). Chest-related symptoms were consistent with changes in the intoxication intensity. Thus, the clinical effectiveness of standard chemotherapy in patients with tuberculosis relapse was significantly lower than in patients with newly diagnosed pulmonary tuberculosis.

Table 2. Cessation of intoxication syndrome in two groups of patients

Cessation after a month	No (%) of patients		p
	Group 1 (n = 96)	Group 2 (n = 83)	
One (the first)	18 (18.7)	32 (38.6)	0.003
Four	38 (39.6)	44 (53.0)	0.074
Eight	24 (25.0)*	1 (1.2)*	<0.001

*The remaining patients experienced treatment failure or they died
Group 1, pulmonary tuberculosis relapse; Group 2, newly diagnosed pulmonary tuberculosis

Post-treatment results of bacteriological examination

An analysis of bacterial loads in the patients with tuberculosis revealed higher MTB loads in patients with tuberculosis relapse that in the 2 group. The patients from the group 2 were mainly characterized by either sputum acid-fast bacilli smear negativity or "+" positivity, while in the patients from group 1 higher bacterial loads were observed ("+++"). The same trend was revealed when culture methods were used. In particular, in group 1 MTB triple and quadruple positivity was mainly detected bacteriologically, while this parameter was either "1+" or "2+" in the 2 group (Table 3).

Table 3. Sputum and bronchoalveolar lavage fluid (BALF) smear and sputum acid-fast bacilli /*MTB* positivity in two groups of patients

Method	No (%) of patients		p
	Group 1 (n = 114)	Group 2 (n = 126)	
Microscopy: smear			
Negative	6 (5.2)	21 (16.6)	0.005
Single positive (+)	27 (23.7)	51 (40.5)	0.006
Double positive (++)	28 (24.6)	32 (25.4)	0.886
Triple positive (+++)	53 (46.5)	22 (17.5)	<0.001
Bacteriology: Sputum and BALF colony number			
Solitary	2 (1.7)	14 (11.2)	0.003
Single positive (1+)	21 (18.4)	44 (34.9)	0.004
Double positive (2+)	36 (31.6)	47 (37.3)	0.354
Triple positive (3+)	27 (23.7)	11 (8.7)	0.001
Quadruple positive (4+)	28 (24.6)	10 (7.9)	<0.001

Group 1, pulmonary tuberculosis relapse; Group 2, newly diagnosed pulmonary tuberculosis

As for the outcomes of sputum smear microscopy, acid-fast bacilli stain conversion in group 1 occurred statistically significantly (p<0.001) later than in patients with newly diagnosed pulmonary tuberculosis. In particular, the mean time to smear conversion was 96.6±6.5 days in 82 patients with tuberculosis relapse (out of 114, 11 patients died and 21 had the treatment failed) and 63.8±4.5 days in 111 patients from group 2 (out of 126, six patients died and nine had the treatment failed).

Almost the same dynamics was observed when evaluating the outcomes of bacteriological tests. Sputum culture conversion in the patients from group 2 was more likely than in patients from group 1. Thus, mean time to sputum culture conversion was 85.5±5.4 days in patients with tuberculosis relapse (n=82) and 56.2±3.6 days in group 2 (n=111), respectively (p<0.001). There was no statistically significant difference between the outcomes of bacteriological culture and microscopic tests. Furthermore, some patients experienced sputum bacteriological culture conversion prior to smear conversion. It can be assumed that this is due to the presence of nonviable MTB during microscopy.

Post-treatment chest X-ray examination

It is important to note that the most important criteria characterizing the treatment effectiveness in patients with pulmonary tuberculosis are cavity closure and disappearance of infiltrative changes (Table 4).

Table 4. Time to cavity closure for two groups of patients

Months after the beginning of treatment	No (%) of patients with cavity		p
	Group 1 (n=102)	Group 2 (n=104)	
Cavity closure after four months	31 (30.4)	56 (53.8)	<0.001
Cavity closure after eight months	37 (36.3)	29 (27.9)	0.198
Cavity was presented after the eighth month	34 (33.3)	19 (18.3)	0.014

Group 1, pulmonary tuberculosis relapse; Group 2, newly diagnosed pulmonary tuberculosis

A total of 206 patients with tuberculosis experienced a destructive process in the lungs. Cavities were observed in 102 (89.5%) patients with tuberculosis relapse and in 104 (82.5%) with newly diagnosed pulmonary tuberculosis (p=0.121). Cavern closure more likely occurred in the patients with newly diagnosed pulmonary tuberculosis than in group 1 (81.7% versus 66.7%), e.g. destruction was present after eight months of the treatment in 19 (out of 104; 18.3%) patients with newly diagnosed tuberculosis compared to 34 (out of 102; 33.3%) patients with TB relapse (p=0.014) (Table 4).

As for the time to disappearance of infiltrative and focal changes, its values were almost indistinguishable from the time necessary for cavity closure with an exception of solitary cases when infiltration disappeared before cavern closure, or, conversely, when pulmonary tissue infiltration persisted for a while.

Treatment outcome

Despite statistically insignificant results of the comparison of death rates and other treatment outcomes, such as lost to follow-up and the treatment completed, a statistically significant difference between the groups studied in terms of such outcomes as cured and the treatment failed was observed. Therefore, tuberculosis relapse was characterized by lower rates of cured patients (39; 34.2%) and higher rates of the patients with treatment failure (21; 18.4%) compared with patients from group 2 (74; 58.7% and 9; 7.1%, respectively) (Table 5).

Table 5. Multidrug resistant tuberculosis (MDR-TB) treatment outcomes

Treatment outcome	No (%) of patients		p
	Group 1 (n = 114)	Group 2 (n = 126)	
Died	11 (9.6)	6 (4.8)	0.149
Treatment failed	21 (18.4)	9 (7.1)	0.008
Lost to follow-up	24 (21.1)	20 (15.9)	0.299
Treatment completed	19 (16.7)	17 (13.5)	0.489
Cured	39 (34.2)	74 (58.7)	<0.001

Group 1, pulmonary tuberculosis relapse; Group 2, newly diagnosed pulmonary tuberculosis

DISCUSSION

The analysis of patients with tuberculosis relapse revealed that among patients with newly diagnosed pulmonary tuberculosis 32.4% were diagnosed until 2014, while 67.6% started suffering from the disease after 2014. After analysing various factors that could affect this parameter, we found that until 2014 these patients with newly diagnosed pulmonary tuberculosis had received an eight-month course of chemotherapy for the first time, whereas after 2014 all patients had undergone a six-month-long tuberculosis treatment. In this case, the duration of the treatment is supposed to be a factor that can prevent tuberculosis relapse. This conclusion is consistent with findings reflected in other researches (5,8), albeit the negative impact of a long-lasting course of chemotherapy on the occurrence of tuberculosis relapse has been emphasized in some studies (14). Thus, it is worth considering the occurrence of new cases of tuberculosis relapse in patients with resistant forms of tuberculosis in response to the implementation of new short-term treatment regimens recommended by the WHO (15). Moreover, the most effective treatment re-

gimen to reduce the probability of relapse in the at-risk group of patients has not been determined by clinical trials (16). Recent studies have shown that long-term treatment reduces the relapse rate in patients with newly diagnosed pulmonary tuberculosis (17). Other studies have demonstrated that short-term chemotherapy regimens increase the incidence of tuberculosis relapse (18). Implementation of novel innovative prolonged chemotherapy regimens for patients with tuberculosis relapse seems to be of vital importance for reaching more favourable treatment outcomes (19,20).

When evaluating the effectiveness of treatment in the patients with tuberculosis relapse based on clinical and morphological changes, more pronounced symptoms of intoxication were observed compared with patients with the primary disease or newly diagnosed pulmonary tuberculosis (8,21). Our findings corroborate this conclusion. Moreover, it has been reported that the prevalence of the pathological process in patients with tuberculosis relapse is higher with the presence of more caverns in the lungs, evidenced by radiographic examination, than in patients with newly diagnosed pulmonary tuberculosis (8,21). However, authors did not take into account MTB resistance to anti-tuberculosis drugs. Nevertheless, some authors (22,23) argue that there is no statistically significant difference in tuberculosis symptoms in patients with relapse compared to those with newly diagnosed pulmonary tuberculosis.

As for the evaluation of sputum bacterial loads and treatment effectiveness by the presence of MTB in sputum, most authors (23,24) indicate that more massive bacterial loads and later sputum culture conversion were observed in patients with tuberculosis relapse than newly diagnosed pulmonary tuberculosis, which is consistent with our findings.

Furthermore, there is some evidence (25,26), including results presented in this study, that the effectiveness of anti-tuberculosis therapy in patients with tuberculosis relapse is much lower than in patients with newly diagnosed pulmonary tuberculosis. However, we have noticed that in all studies there was no evaluation of the treatment effectiveness and outcomes in patients with MDR-TB relapse.

In conclusion, standard treatment effectiveness for the patients with MDR newly diagnosed pulmonary tuberculosis usually manifests by a faster improvement and stabilization of health, less intense bacterial secretion in sputum, earlier smear conversion, higher frequency of cavity closure and achievement of clinical and radiological improvements, more cases of cured patients and less common treatment failures compared with multidrug-resistant tuberculosis relapse.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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