Original Article

Effectiveness of Anti-Tuberculosis Chemotherapy in Patients with Tuberculosis Relapse Compared with Newly Diagnosed Patients

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Abstract

Background: To study the effectiveness of antituberculosis chemotherapy in patients with relapse pulmonary tuberculosis (RTB) compared with patients with the newly diagnosed process. **Methods:** We examined 285 TB patients, including 126 individuals with RTB (Group 1) and 159 patients with newly diagnosed pulmonary tuberculosis (NDPTB) (Group 2). All patients were diagnosed with infiltrative PTB. Effectiveness of the basic course of antimycobacterial treatment was assessed in accordance with the following data: time required for the normalization of clinical manifestations, smear conversion, cavity healing, disappearance of infiltrative and focal changes in the pulmonary tissue, as well as the final clinical effectiveness of therapy. **Results:** Disappearance of clinical symptoms was statistically significantly faster in Group 2 compared with RTB patients in 2.25 ± 0.11 and 3.40 ± 0.15 months, respectively ($P < 0.001$). Sputum culture conversion was observed after 6 months of treatment in 138 (86.79%) patients with NDPTB and 89 (72.22%) patients from Group 1 ($P = 0.0023$). Closure of cavities and disappearance of infiltrative and focal changes in the lungs occurred within 6 months of chemotherapy only in 55 (43.65%) patients with RTB and 93 (58.49%) patients with NDPTB ($P = 0.0133$). **Conclusions:** Standard treatment for patients with NDPTB is considered successful in case of faster health improvement and stabilization, less pronounced rates of toxic adverse reactions to antiTB drugs, faster sputum smear and culture conversion and cavity healing, signs of clinical and radiological convalescence, and the reduced number of large residual changes after the treatment compared with RTB.

Keywords: Pulmonary tuberculosis relapse, treatment, tuberculosis, tuberculosis treatment effectiveness

INTRODUCTION

Tuberculosis (TB) is one of the ten leading causes of death worldwide. In 2017, 10 million people were diagnosed with TB and 1.6 million died of it.[1] TB relapse (TB) is of huge importance in the field. According to some reports, the rate of relapses ranges significantly and is estimated to vary from 4.9% to 47%. Such variability is due to differences in the regional epidemiology of TB recurrences and definitions used by various anti-TB programs.[2] In Ukraine, despite the stabilization of the basic morbidity rates, the epidemiological situation with TB is fairly complicated mainly due to an increase in the amount of resistant TB cases in the structure of pulmonary TB (PTB) morbidity.[3,4] In addition, data analysis has shown that an increase in the morbidity rate is primarily observed as a result of RTB.[5] According to some authors,[6] relapses are considered to be the cause of chemoresistant TB, including extensive (XDR) and multidrug-resistant (MDR) TB, which is registered several times more frequently than in patients with primary TB.

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Moreover, RTB is of vital importance due to the fact that the prevalence of TB recurrence in patients successfully treated from active TB has been remaining constantly high for many years.[7] It has been reported that relapses often occur after the successful treatment of the firstly diagnosed TB.[8]

A higher prevalence of RTB is observed not only in Ukraine but also in other TB-affected countries.[2,9] In particular, there is strong evidence that the high incidence of TB corresponds to a high rate of relapses.[10] The intensive rate of relapses and their more noticeable role in the formation of the cohort of TB patients have been registered.[11] This may indicate the significant role of sputum-positive patients with RTB in the further transmission of the disease, especially among children.[2]

There are two hypotheses that explain the development of RTB. According to the endogenous hypothesis, *Mycobacterium tuberculosis* (MBT) is reactivated in residual foci, whereas the exogenous theory states that the massive amount of MBTs enters the body from the outside (superinfection).[12]

It is believed that the reactivation of latent MTBs may depend on their size and activation status, which is simultaneously influenced by the form and phase of the specific process. RTB development is dependent on the ability of MBTs to survive as inactive forms under unfavorable circumstances and get activated in improved conditions. It is worth noting that this may occur as a consequence of some changes in the immune system and in the structure of the residual pathological foci.[13,14] In addition, the activation of latent MBTs occurs against the background of the compromised immune system due to social reasons, concomitant diseases, etc.[15,16] Thus, residual changes contribute to a higher RTB prevalence.

However, social risk factors such as poverty, the spread of TB in prisons, homelessness, and occupational hazards are believed to be the major reasons for the development of RTB. Political and economic crises accompanied by the steep decline in the welfare of citizens cause mental stress that leads to malnutrition, which may contribute to RTB development.[17]

Nowadays, there are many immunological tests that are used to determine the TB activity, but these methods cannot be used to detect the latent MBT forms in residual post-TB foci.[18,19]

Despite the impart of endogenous etiology in RTB, the reinfection theory remains of huge importance because a potential patient with RTB who is in constant contact with contagious MBT sputum-positive patients has the risk of getting the disease up to ten-fold higher than if such contact is absent.[20]

Little is reported on the effectiveness of treatment for patients with RTB and newly diagnosed PTB (NDPTB), although we have noticed some changes in clinical practice, which inspired this study.

Thus, the aim of our research was to study the effectiveness of anti-TB chemotherapy in patients with RTB compared with those diagnosed with NDPTB.

METHODS

In this study, 285 PTB patients, including 126 patients with TB relapse (Group 1) and 159 patients with NDPTB (Group 2) aged between 20 and 70 years, were enrolled. The inclusion period lasted from 2011 to 2014.

Randomization was performed to provide equal distribution of baseline characteristics, namely, age, gender, height, body weight, and comorbidities [Table 1].

Active PTB was verified by a medical history and clinical findings compatible with TB, chest X-ray examination showing lung involvement, smear acid-fast bacillus (AFB) positivity, and sputum MBT culture positivity.

One of the criteria for distributing the patients between the groups was the presence of drug resistance. The total amount of patients with MDR, pre-XDR, and XDR TB in Group 1 reached 44 (34.92%) individuals and 46 (28.93%) individuals in Group 2. It is important to note that the difference in the number of patients with MDR TB from both groups was found to be statistically insignificant ($P = 0.2809$). This was evaluated to exclude the impact of MDR-TB in this study.

We evaluated the effectiveness of the basic course of anti-TB chemotherapy according to the following data: time necessary for the normalization of TB clinical manifestations, sputum smear conversion, healing of cavities, disappearance of infiltrative and focal changes in pulmonary tissue, as well as the final clinical efficacy of therapeutic measures.

Table 1: Baseline characteristics of patients with pulmonary tuberculosis

Characteristics	Group 1 (*n*=126), *n* (%)	Group 2 (*n*=159), *n* (%)	*P*
Age	44.39±0.91	45.58±0.90	0.3620
Males	104 (82.54)	128 (80.50)	0.6606
Females	22 (17.46)	31 (19.50)	0.6606
Height, cm	165.80±1.48	165.6±0.82	0.910
Weight, kg	55.92±0.72	56.82±0.74	0.397
Respiratory comorbidities*	22 (17.46)	24 (15.09)	0.5895
Cardiovascular comorbidities	39 (30.95)	50 (31.45)	0.9280
Gastrointestinal comorbidities	22 (17.46)	22 (13.84)	0.4016
CNS-related comorbidities	18 (14.29)	22 (13.84)	0.9136
Comorbidities that affect the urinary tract	2 (1.59)	2 (1.26)	0.8144
Rheumatic diseases	2 (1.59)	0	-
Diabetes mellitus	5 (3.97)	4 (2.52)	0.4877
Psoriasis	1 (0.79)	0	-
HIV infection	2 (1.59)	1 (0.63)	0.4314
Syphilis	1 (0.79)	1 (0.63)	0.8724
Chronic alcohol use disorder	6 (4.76)	5 (3.14)	0.4811

*Concomitant diseases were combined in many patients. CNS: Central nervous system

Treatment regimen

Treatment of patients was complex and individualized. Before obtaining information on the outcomes of MBT sensitivity bacteriological tests, all patients were administered the combination of 4–5 anti-TB drugs (isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and/or streptomycin (S) during the intensive phase lasting for the first 2 months. Indications for S prescription were the patient's severe condition, significant sputum culture positivity, the presence of specific changes in the lungs, and numerous destructive changes. Then, S was cancelled, or the maintenance phase was provided, or the patients the treatment with the medicines outlined above was continued for another month due to no smear conversion, and/or huge TB-affected areas and/or multiple cavities whose size exceeded 3 cm. In case of smear AFB positivity, the intensive phase was prolonged to 120 doses or the treatment was considered "ineffective." Anti-TB drugs were procured via the Ukrainian centralized national supply system.

After 60 doses in case of the elimination of TB symptoms and sputum conversion, H, R, and E or Z were prescribed daily for 3 months at the continuation phase. Then, E or Z was cancelled, whereas the treatment with H and R for the other 2 months was continued on a daily basis or three times a week for 2 months.

If mycobacterial resistance was found, the corresponding chemotherapy was prescribed to the patients. However, the treatment with the first-line drugs could last for up to 10 weeks due to the availability of data based only on the Lowenstein–Jensen (LJ) method at that time.

Laboratory evaluation

A standard microbiological examination of a sputum smear stained by the Ziehl–Neelsen method and culture using the LJ medium was conducted prior to the enrollment in the study, on day 60, day 90, and day 180 after the beginning of the treatment. Isolates of MTBs were tested for sensitivity to the first- and second-line anti-TB drugs using commercially available kits (Tulip Diagnostics Pvt. Ltd., Goa, India).

Sputum culture was performed for all patients, whereas sputum smear microscopy was not carried out in some patients of both groups. Sputum and bronchoalveolar lavage fluid MBT positivity rate was evaluated in accordance with literature.[21]

X-ray examination

Pathological features (e.g., the severity of the disease and changes in the localization of the process in lungs) were assessed via X-ray examination. Chest X-ray examination (two views) was performed in case of pathological findings. Targeted computed tomography (CT) scanning of the destructed areas was carried out in every patient. Interpretation of chest X-ray results allowed us to verify TB diagnosis and to evaluate localization, severity, and peculiarities of PTB cavities. According to radiological findings, all patients suffered from infiltrative PTB with the same size of lung areas involved in the pathological process in both groups ($P > 0.05$), which was a group inclusion criterion [Table 2].

Table 2: Tuberculosis localization and degree of diffusion in subgroups 1 and 2

Localization and degree of diffusion	Group 1, n (%)	Group 2, n (%)	P*
One to two segments	19 (15.08)	28 (17.61)	0.5681
One pulmonary lobe	23 (18.25)	34 (21.38)	0.5123
Two pulmonary lobes	32 (25.40)	41 (25.79)	0.9403
One lung	46 (36.51)	49 (30.82)	0.3124
Two lungs	6 (4.76)	7 (4.40)	0.8851

*Differences between two independent variables were considered statistically significant at $P<0.05$

Radiological examination (chest X-ray and CT scans) was performed after the intensive phase usually after 2–3 months, then each 2 months till 6 months of the patients' treatment in the hospital.

Statistical evaluation

Statistical analyses were performed using a StatSoft, Inc., Tulsa, OK.: STATISTICA Version 8, 2007, Oklahoma, USA and *Excel* applications. The obtained data were statistically analyzed using a standard parametric Student's *t*-test,[22] which was chosen after performing the Shapiro–Wilk and Kolmogorov–Smirnov normality tests. The difference was considered to be statistically significant at $P < 0.05$.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Kharkiv National Medical University, Kharkiv, Ukraine (#9/December 3, 2014).

RESULTS

The time required for normalization of the most important TB clinical manifestations and the routinely determined parameters under the influence of standard chemotherapy was evaluated based on the disappearance of intoxication and chest symptoms. The intoxication symptom was considered to be terminated in the presence of subjective signs in patients such as improved appetite, no general weakness, fatigue, sweating, normalization of body temperature and body weight, and changes in urinalysis, evaluated as symptoms of TB intoxication. The improvement signs concerning chest symptoms included the disappearance of shortness of breath, cough, chest pain, hemoptysis, and pulmonary hemorrhages.

Thus, the intoxication syndrome was not registered after the 1st month of treatment in 16 (19.28%) out of 83 RTB patients and in 34 (49.28%) out of 69 patients with NDPTB. It is worth noting that this parameter was statistically significantly higher in Group 2 than in Group 1 ($P < 0.001$). After the 3-month-long treatment, the intoxication syndrome was completely eliminated in 61 (88.41%) out of 69 patients with NDPTB. Meanwhile, only 44 (53.01%) out of 83 patients with RTB succeeded in achieving the cessation of intoxication syndrome ($P < 0.001$). After 6 months of chemotherapy, intoxication was absent in all patients from the control group (100.00 ± 0.01) (Group 2)

and 72 (86.75%) of 83 patients from Group 1 ($P < 0.001$). Thus, the elimination of intoxication symptoms was observed statistically significantly earlier in the patients from Group 2 than in the patients with RTB.

Chest symptoms corresponded to changes in intoxication. Therefore, the disappearance of this clinical symptomatology was significantly lower in the patients with RTB. Chest symptoms were eliminated in the patients with NDPTB on an average after 2.25 ± 0.11 months, whereas the patients with RTB required 3.40 ± 0.15 months ($P < 0.001$).

Thus, the clinical effectiveness of standard chemotherapy in patients with RTB (Group 1) was significantly lower than in patients with NDPTB (Group 2).

The study of anti-tuberculosis drugs (ATD) side effects is considered to be an important problem in treating TB. We divided all adverse reactions to ATDs that we had observed in our patients into toxic (toxic hepatitis, cardiotoxicity, neurotoxicity, etc.), allergic (allergic dermatitis or other allergic manifestations), and mixed (toxic and allergic manifestations). Adverse reactions to ATDs during the treatment were observed in 157 (55.09%) patients with PTB, including 76 (60.32%) patients from Group 1 and 81 (50.94%) patients from Group 2. It is worth mentioning that the difference was statistically insignificant ($P = 0.1150$). However, we revealed that allergic ATD-related side effects were registered 2.27 times higher in patients with NDPTB compared with Group 1 (1st group – 16 [12.70%], 2nd group – 46 [28.93%], $P = 0.0011$). Having analyzed the toxic effects of ATDs in patients with RTB, the opposite situation was revealed (1st group – 46 [36.51%], 2nd group – 19 [11.95%], $P < 0.001$). The rate of toxic side effects to ATDs was 3.05 times in RTB patients than in those with NDPTB. As for the mixed side effects of ATDs, the difference between Group 1 and Group 2 was statistically insignificant (1st group – 14 [11.11%], 2nd group – 16 [10.06%], $P = 0.7744$).

Analysis of sputum smear and culture positivity in patients with TB [Table 3] revealed that the amount of AFBs in sputum smears and the number of MBT colonies on the LJ medium were higher in patients with RTB compared with the control group. In addition, sputum smear conversion is known to be one of the most important criteria that characterize the effectiveness of chemotherapy in patients with PTB. The number of smear AFB-positive patients upon admission to the hospital was higher in patients with NDPTB than in Group 1. Information on sputum conversion among patients from Groups 1 and 2 is available in Table 4. Furthermore, as shown in Table 4, sputum smear conversion in patients of both groups mainly occurred during the 2nd and 3rd months of chemotherapy. However, smear AFB conversion in Group 1 was registered later compared with patients with NDPTB. Moreover, the percentage of sputum smear positive patients after 6 months of chemotherapy was also statistically significantly higher in patients with recurrent PTB (Group 1) than in NDPTB.

Almost the same dynamics was observed when evaluating the treatment outcome by the bacteriological method [Figure 1]. As shown in Figure 1, sputum culture conversion in patients from Group 2 occurred at a higher rate compared with patients from Group 1. In particular, after 2 months of the chemotherapy, sputum culture conversion was achieved in 126 (79.25%) patients from Group 2 and in 71 (56.35%) patients from Group 1 ($P < 0.001$). After 3 months of treatment, culture conversion occurred in 137 (86.16%) patients with NDPTB and in 82 (65.08%) patients with RTB ($P < 0.001$). Six months later, 138 (86.79%) patients with newly diagnosed PTB (NDPTB) achieved sputum culture conversion. At the same time, this parameter was statistically significantly lower in patients with RTB. It was found that 89 (72.22%) patients became sputum culture negative ($P = 0.0023$). Thus, both smear and sputum culture conversion is observed more frequently in patients with RTB than in patients with NDPTB against the background of chemotherapy.

Table 3: Sputum and bronchoalveolar lavage fluid smear and sputum acid-fast bacilli/*Mycobacterium tuberculosis* positivity in Groups 1 and 2

Number of AFB per fields	Microscopic study		
	Group 1, *n* (%)	Group 2, *n* (%)	*P**
Smear negative (AFBs are not found in 100 fields)	22 (17.46)	64 (40.25)	<0.001
Smear single positive; "+" (10-99 AFBs per 100 fields)	14 (11.11)	68 (42.77)	<0.001
Smear double positive; "++" (1-9 AFBs per fields)	43 (34.13)	18 (11.32)	<0.001
Smear triple positive; "+++" (over 10 AFBs in each fields)	47 (37.30)	9 (5.66)	<0.001
Number of MBT colonies on the medium	**Bacteriological study**		
	Group 1, *n* (%)	Group 2, *n* (%)	*P**
Solitary colonies	10 (7.94)	36 (22.64)	0.0009
Sputum and BALF MBT single positive; "1+" (20-100 colonies)	19 (15.08)	84 (52.83)	<0.001
Sputum and BALF MBT double positive; "2+" (100-200 colonies)	48 (38.10)	26 (16.35)	<0.001
Sputum and BALF MBT triple positive; "3+" (200-500 colonies [almost totally covered])	37 (29.37)	10 (6.29)	<0.001
Sputum and BALF MBT quadruple positive; "4+" (over 500 colonies [totally covered])	12 (9.52)	3 (1.89)	0.0045

*Differences between two independent variables were considered statistically significant at *P*<0.05. BALF: Bronchoalveolar lavage fluid, AFBs: Acid-fast bacillus, MBT: *Mycobacterium tuberculosis*
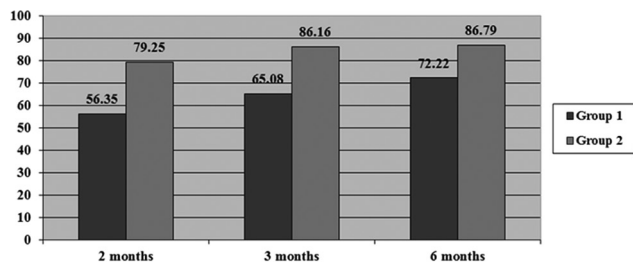
Figure 1: Sputum conversion rate depending on the treatment duration (in %)

In addition, disappearance of cavities and infiltrative changes is one of the most important criteria that characterize the effectiveness of TB treatment [Table 5].

In this study, 196 patients with PTB with the destructive process were enrolled. Out of them, cavitation was observed in 91 (72.22%) patients with RTB and 105 (66.04%) patients with NDPTB. No statistically significant difference between Groups 1 and 2 was revealed ($P = 0.2645$).

We studied the dynamics and features of cavity healing in the lungs of patients from both groups. As show in Table 5, in both groups, the cavity cure mainly occurs after 2–5 months of treatment. In particular, cavities in patients with recurrent TB were healed after 4–5 months of treatment to a significantly lesser extent than in patients with NDPTB. The same trend was observed for up to 6 months of chemotherapy. After 6 months of treatment, cavitation was still present in almost one-third of patients in Group 1 and in 7.55% patients from Group 2.

As for the time required for the disappearance of infiltrative and focal changes, it practically did not differ from the terms of cavity healing. The only exception was observed in some isolated cases where infiltration disappeared before cavity healing, or *vice versa*, when the inflammation of the pulmonary tissue continued for a while after healing.

The direct treatment effectiveness would be incompletely reflected if we did not evaluate the features of residual changes after the completion of the main course of antimycobacterial therapy in both groups.

Large residual changes were observed statistically significantly less frequently in 131 (82.39%) patients with NDPTB than in RTB (122 [96.83%] patients, $P = 0.0002$). The opposite situation was revealed while comparing small residual changes. They were observed in 4 (3.17%) individuals with RTB and in 28 (17.61%) patients with NDPTB. The difference between both groups was statistically significant ($P = 0.0002$).

DISCUSSION

The prevalence of RTB in TB-affected countries remains high.[9] According to the RTB-related clinical and morphological changes, it has been reported[23] that the intoxication symptoms are more pronounced in this cohort of patients compared with those with the newly diagnosed disease, which is consistent

Table 4: Sputum and bronchoalveolar lavage fluid smear conversion rates

Stages of treatment	Absolute number (%)		P*
	Group 1	Group 2	
Positive Ziehl-Neelsen staining upon admission	104 (100)	95 (100)	-
Two months	60 (57.67)	75 (78.95)	0.0016
Three months	74 (71.15)	85 (89.47)	0.0015
Six months	85 (81.73)	91 (95.79)	0.0022
Smear AFB positive patients after 6 months	19 (18.27)	4 (4.21)	0.0022

*Differences between two independent variables were considered statistically significant at $P<0.05$. AFB: Acid fast bacilli

Table 5: Cavity cures and disappearance of infiltrative changes in lungs

Stages of treatment	Absolute number (%)		P*
	Group 1	Group 2	
Two to three months	29 (23.02)	43 (27.04)	0.4386
Four to five months	42 (33.33)	76 (47.80)	0.0144
Six months	55 (43.65)	93 (58.49)	0.0133
Destruction is present after the 6-month-long treatment	36 (28.57)	12 (7.55)	<0.001

*Differences between two independent variables were considered statistically significant at $P<0.05$

with our findings. At the same time, we believe that the distribution of groups in that study[23] was not randomized. In this study, the patients with RTB were characterized by a more widespread process with a higher number of cavities in the lungs, evidenced by chest X-ray results, than in patients with NDPTB. Our findings showed the same distribution of TB process in the lungs. However, some authors[24] do not report a significant noticeable difference in the symptoms of TB in patients with relapse compared with NDPTB.

As for the sputum positivity and treatment effectiveness in smear AFB positive patients, most authors[25] have noticed that sputum conversion in patients with relapsed TB is delayed than in NDPTB (62%–87%), which is also observed in our study.

In addition, some authors point out[26,27] that the effectiveness of anti-TB therapy in RTB patients is significantly lower than in patients with NDPTB. This is consistent with our findings. Anti-TB treatment outcome has a trend to worsen worldwide.[28]

Recently, the short-term treatment regimens for TB patients have gained popularity. In this case, the relapse is no exception. Our findings suggest that the current standards of treatment for RTB patients should be modified because patients with recurrent TB experience symptoms of intoxication, persistent sputum positivity for Ziehl–Neelsen stain, and destruction and infiltration for a long time, and therefore the intensive phase should last longer until the effectiveness of treatment is observed. In addition, it has been reported that the most

effective treatment regimen to reduce the probability of relapse in patients who are at high risk of recurrence has not been determined in clinical trials.[2] Recent studies have shown that the long-term treatment reduces the probability of relapse in patients with NDPTB.[29] There is also some evidence that the short-term chemotherapy regimens contribute to an increase in the incidence of RTB.[30] The implementation of novel, innovative long-term chemotherapy regimens for patients with TB is of great importance for achieving the better treatment outcomes.

CONCLUSIONS

It is worth noting that the effectiveness of standard treatment for patients with NDPTB usually manifests by a faster improvement and stabilization of patients' health, a lower prevalence of toxic adverse effects of anti-TB drugs, faster sputum smear and culture conversion, a higher rate of cavity cures and clinical and radiological signs of convalescence, and a reduced rate of significant residual changes observed after the treatment compared with RTB. Our findings suggest that the patients with RTB require more prolonged chemotherapy (than stated in standard treatment regimens in Ukraine) compared with the patients with NDPTB. This prolongation of chemotherapy can result in a more pronounced clinical and radiological stabilization of the process in this cohort of patients.

Acknowledgments

Conflicts of interest
There are no conflicts of interest.

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