Yurii Feshchenko[1], Dmytro Butov[2], Mykhailo Kuzhko[1], Mykola Gumeniuk[1], Tetiana Butova[3]

[1]SO "National Institute of phthisiology and pulmonology named after F. G. Yanovskyi NAMS of Ukraine", Kyiv, Ukraine.
[2]Kharkiv National Medical University, Kharkiv, Ukraine
[3]V. N. Karazin Kharkiv National University, Kharkiv, Ukraine

Efficacy and safety of intravenous chemotherapy during intensive treatment phase in patients with newly diagnosed pulmonary tuberculosis

The authors declare no financial disclosure

Abstract

Introduction: The purpose of our study was to examine the efficacy and safety of intravenous chemotherapy during intensive treatment phase in patients with newly diagnosed pulmonary tuberculosis (pulmonary TB).

Material and methods: The study involved 92 patients with newly diagnosed pulmonary TB aged between 20 and 68. All patients with newly diagnosed pulmonary TB and chemosensitive tuberculosis were enrolled in the study. The patients were allocated to two groups. The first (control) group of 46 patients received standard chemotherapy orally. The second (main) group consisted of 46 patients who were prescribed isoniazid, rifampin, ethambutol by i.v. infusion, and pyrazinamide orally as a part of the standard treatment.

Results: Symptoms of intoxication and chest manifestations in pulmonary TB patients from the second group were eliminated faster than the same symptoms in the group 1. In the group 2, the mycobacterial clearance in sputum smears was achieved more rapidly, and up to 2 months it was reached in 37 patients (80.43%), while in the control group in 25 patients (54.35%), p = 0.0066. Destruction healing and inflitrative change alleviation after 4 months was reached in 38 patients (82.61%) (in control group — 28 (60.87%), (p = 0.0192). No additional negative effects were detected when compared with the control group at any time.

Conclusions: Thanks to i.v. chemotherapy, clinical manifestations of the in-patients with pulmonary TB were eliminated faster, severe side effects of anti-TB drugs were not noticed, time of bacterial clearance and healing of destruction was shorter, healing frequency of destructions increased and the of residual changes decreased.

Key words: tuberculosis, treatment of tuberculosis, intravenous treatment of tuberculosis, antituberculous drugs

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Introduction

Tuberculosis (TB) continues to hold a dominant position among frequent infections, constituting a threat to the population of most countries, including the economically developed ones [1]. TB problem is extremely important in Ukraine, where since 1995 it has been registered an epidemic, and although the growth rate of morbidity and mortality from TB has been stabilized in recent years, the situation still remains difficult.

Despite the reduction in the growth of total incidence rate, prevalence and mortality from TB for the last 5 years remain high and exceed 2–3 times the epidemic threshold [1, 2].

The most prominent achievements of phthisiology are associated with the development of antimycobacterial therapy. Performance targets for further improvement of the newly diagnosed pulmonary TB treatment determine not only the increasing of destructions closure frequency and negation of sputum, but also the use of therapies

that can achieve sustainable results within shorter time without forming large residual changes in the lungs [3–5].

Modern methods of controlled therapy represent programmable treatment [6]. Foreign and domestic experience of DOTS program implementation has shown that treatment standardization and control procedures of its effectiveness are not always justified [7, 8]. The success of the used therapy depends with great frequency on the possibility to apply a full course of chemotherapy, namely the administration of the required number of drugs in adequate doses for the necessary duration of treatment [9, 10].

However, there remains a certain percentage of patients for whom this method of treatment does not lead to significant improvement of health. This generalized treatment method does not consider the presence of comorbidities and development of side effects of therapy, which require treatment correction [11]. Despite the high level of scientific and practical justification of existing standards of TB chemotherapy, its further improvement is necessary [12, 13].

The lack of therapeutic effect may be caused by the development of drug resistance [14], the inability to create optimal concentrations of the drugs in the blood and tissues [15] as a result of their incomplete absorption in the gastrointestinal tract [16] and accumulation in the inflammation area [4, 17], or rapid inactivation of the drugs [18].

In the course of clinical and experimental studies it was found that the therapeutic effect of ATD (anti- TB drugs) is directly related to the concentration of a drug in the blood, and therefore to the area of specific inflammation [19, 20]. According to the literature, there are some data about the use of intravenous (i.v.) chemotherapy in patients with TB meningitis. Those figures show that this type of intensive treatment reduces mortality of patients with TB meningitis [21]. In addition, effectiveness of i.v. chemotherapy for patients with TB and deficit of absorption have been also shown [22].

All this determines the search for ways to improve the treatment of patients with newly diagnosed pulmonary TB by optimization of the intensive phase of TB chemotherapy with i.v. use of ATD.

Thus, the purpose of our research was to study the effectiveness and safety of intravenous chemotherapy in the intensive phase of treatment of patients with newly diagnosed pulmonary TB (pulmonary TB).

Material and methods

Patients

This prospective, randomized, comparative study was conducted in SO "National Institute of phthisiology and pulmonology named after F. G. Yanovskyi NAMS of Ukraine", Kyiv and Kharkiv National Medical University, Kharkiv, Ukraine.

The study involved 92 patients with pulmonary TB aged between 20 and 68 . The period of inclusion of patients in the study was from 2011 to 2017. All patients with pulmonary TB and chemosensitive TB were enrolled in the study. Patients were randomly allocated by computer-generated sequence into two groups. The first (control) group of 46 subjects received standard chemotherapy orally. The second (main) group consisted of 46 patients who were prescribed isoniazid, rifampin, ethambutol in standard dose by i.v. infusion, as a part of the standard treatment.

The randomization resulted in equal distribution of baseline characteristics: age, gender, height, body weight, comorbidities, serum biochemistry parameters, severity and various manifestations of the disease (Tables 1–3).

Active pulmonary TB was defined by a medical history and clinical findings compatible with TB, a chest X-ray showing lung involvement, and a positive sputum smear for acid-fast bacilli and positive culture for MTB. On the patients' admission to hospital, infiltrative pulmonary TB was the most common type and was observed in every patient from the first group. In the second group, infiltrative pulmonary TB was observed in 43 (93.48%) patients. Moreover, 3 (6.52%) individuals from the second group were diagnosed with disseminated pulmonary TB. Quantitative characteristics of TB cases within both groups of patients were evaluated and shown to be insignificant (p > 0.05). The difference between the spread of the TB process in the lungs and the number and size of destructions was insignificant (p > 0.05).

Treatment regimen

All patients from the first group received standard chemotherapy, consisting of orally administered isoniazid (0.3 g), rifampin (0.6 g), pyrazinamide (2 g), ethambutol (1.2 g) with a dose reduction after the intensive phase of the therapy. The ATD were procured through the Ukraine's centralized national supply system.

The second group was treated with i.v. chemotherapy, i.e. isoniazid (used in a dose of 100 mg/ml in 5 ml of i.v. (intravenous jet, slowly) — by stream infusion once per day for 60 days starting

on admission to the hospital), rifampin (used in a dose of 600 mg in 20 ml of 0.9% in 200 ml sodium chloride solution i.v. (intravenous drips, slowly) — by drop infusion once per day for 60 days starting on admission to the hospital), ethambutol (used in a dose of 100 mg/ml in 20 ml of 5% in 200 ml glucose solution i.v. (intravenous drips, slowly) — by drop infusion once per day for 60 days starting on admission to the hospital) and pyrazinamide (2 g in tablets orally). Intravenous administration of the ATD was performed in the ulnar vein. Parenteral chemotherapy was performed in the 2nd group only during the intensive phase of treatment (60 doses), and during the continuation phase ATD were taken orally in a standard dosage.

Laboratory evaluation

A standard microbiological examination of a stained sputum smear using the Ziehl-Neelsen and culture Lowenstein-Jensen methods was conducted prior to study entry and on the 30th, 60th, 90th, and 150th day from the start of the treatment. Isolates of MTB were tested for sensitivity to first- and second-line anti-TB drugs with a commercially available kit (Tulip Diagnostics Pvt Ltd., Goa, India). The biochemical parameters were evaluated using standard routine techniques at baseline and repeated 2 months later.

Bacteriostatic blood activity (BBA) was identified in TB patients against the standard laboratory strain of the Mycobacterium tuberculosis (MBT) H37Rv on the liquid Proskauer-Beck medium using the procedure of Rudoy VV [23]. The elements of test-strain film were placed into test-tube and incubated in the thermostat during 10 days. At the presence of growth in the control sample, which covered its entire surface, the results were counted. The level of BBA was estimated according to the greatest blood dilution, where the MBT growth inhibition was observed. The BBA level was considered low in dilutions of 1: 2–1:4; average 1: 8–1:16; high 1:32–1:512.

All patients admitted to the hospital were tested for HIV with the use of rapid tests. All subjects were HIV-negative.

X-ray evaluation

Pathological peculiarities, for example, the severity of the disease and changes in localization, were assessed through X-ray. Chest fluorography was performed in the outpatient department for every subject involved in the study. In cases of pathological findings, we conducted a chest X-ray (two views). Targeted tomography of the destructed area on selected sections was performed in every patient. Interpretation of the thorough X-ray examination allowed us to estimate the first TB diagnosis, specifically, to detect localization, severity, and peculiarities of TB destructions in the lungs.

X-ray monitoring of patients was repeated every 2 months following the start of treatment until the end of the continuation phase (6 months).

Statistical evaluation

The obtained data were statistically analyzed using standard Student t test [24]. The difference was considered to be significant at p < 0.05.

Ethics approval and consent to participate

The project was approved by the Ethics Committee of the SO "National Institute of phthisiology and pulmonology named after F. G. Yanovskyi NAMS of Ukraine", Kyiv, Ukraine. It was conducted according to the Declaration of Helsinki standards. All of the patients gave written informed consent and explicitly provided permission for treatment and blood analyses, as well as for the collection of relevant clinical data.

Results

This study comprised 92 TB patients. The baseline characteristics of patients in the two treatment groups were not statistically different, indicating that the outcome was not biased by sample heterogeneity (Tables 1–3).

Regression of intoxication and chest symptoms were the hallmarks of estimating how rapidly disease manifestation terminates after i.v. chemotherapy administration. Chest symptoms were evaluated through dyspnea, cough, and chest pain reduction or alleviation. Intoxication symptom regression was evaluated regarding subjective symptoms (increased appetite, general revival, fatigue, and sweating alleviation), normalization of body temperature, and body weight, which were considered symptoms of TB intoxication. Data are shown in Table 2. Therefore, in the second group, patients demonstrated more rapid intoxication and chest symptom alleviation than in the first group. Fever is mainly related to the severity of the specific process in the lungs lesions. They attenuated more rapidly in patients of the second group in comparison with the first group, which is explained by the high detoxication effect of i.v. chemotherapy during the treatment. This can be accounted for a low number of side effects of the therapy among the

Table 1. Baseline characteristics of patients with pulmonary TB

Characteristics	Group 1 n = 46	Group 2 n = 46	p-value
Age	42.06 ± 1.20	40.78 ± 1.24	0.4621
Males	36 (78.26%)	32 (69.57%)	0.3425
Females	10 (21.74%)	14 (30.43%)	0.3425
Height, cm	166.2 ± 1.55	162.9 ± 1.52	0.1371
Weight, kg	55.09 ± 1.29	55.78 ± 0.99	0.6710
Co-morbidities*: Diseases of the respiratory system	13 (28.26%)	11 (23.91%)	0.6355
Diseases of the cardiovascular system	19 (41.30%)	21 (45.65%)	0.6745
Diseases of the gastrointestinal tract	7 (15.22%)	9 (19.57%)	0.5829
Diseases of the central nervous system	4 (8.70%)	7 (15.22%)	0.3353
Disease of the urogenital system	2 (4.35%)	3 (6.52%)	0.6469
Rheumatic diseases	2 (4.35%)	2 (4.35%)	1.000
Diabetes	7 (15.22%)	9 (19.57%)	0.5829
Psoriasis	2 (4.35%)	1 (2.17%)	0.5570
Chronic alcoholism	8 (17.39%)	9 (19.57%)	0.7882

*in many patients, concomitant diseases were combined

Table 2. Period of reduction of tuberculosis clinical signs in patients of the groups

Clinical symptoms	Group 1			Group 2			
	No. at the beginning of treatment		Terms of disappearance of clinical signs (months)	No. at the beginning of treatment		p-value#	Terms of disappearance of clinical signs (months)	p-value*
	n	%		n	%			
Intoxication symptoms: Weakness	28	60.87	2.77 ± 0.59	33	71.74	0.2700	1.22 ± 0.36	0.0238
Loss of appetite	10	21.74	2.49 ± 0.75	13	28.26	0.4708	0.87 ± 0.21	0.0298
Fatigue	13	28.26	3.67 ± 0.39	15	32.61	0.6508	2.06 ± 0.41	0.0088
Night sweats	22	47.83	3.41 ± 0.69	25	54.35	0.5323	1.08 ± 0.48	0.0070
Increased body temperature	26	56.52	2.68 ± 1,01	30	65.22	0.3929	0.61 ± 0.39	0.0490
Chest symptoms: Cough	36	78.26	4.89 ± 0.71	38	82.61	0.5987	2.14 ± 0.77	0.0107
Dyspnea	24	52.17	1.89 ± 0.53	27	58.70	0.5294	0.51 ± 0.30	0.0235
Pain in the chest	4	8.70	3.57 ± 0.49	5	13.04	0.5043	1.38 ± 0.51	0.0189

*the p-value is the significance of difference between parameters in Groups 1 and 2 (No. at the beginning of treatment); # the p-value is not the significance of difference between parameters in Groups 1 and 2 (Terms of disappearance of clinical signs)

observed patients of the 2nd group, which is associated with the slow administration of rifampin and ethambutol in a reasonably large amount of solution (400 ml) per day.

When studying the basic biochemical indicators during the treatment (Table 3), we did not find significant changes in the concentration of total bilirubin and protein — these indicators were within normal range either before the treatment or after two months except for the rare cases. However, special attention should be paid to indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations. As shown in Table 3, the TB toxicity in the organisms of patients of the group 2 prior to treatment was higher compared to the 1st group. After

Table 3. Dynamics of the main biochemical parameters in observed patients

Biochemical parameters			Total bilirubin (μmol/l)		ALT (μmol/l)				AST (μmol/l)				Total protein, g/l	
					The parameter increased above normal		Patients with normal ALT parameter		The parameter increased above normal		Patients with normal AST parameter			
Normal parameters			0–20.5		0.1–0.68				0.1–0.45				65.0–90.0	
Group 1	No. on admission	n	46		5		41		7		39		46	
		%	100		10.87		89.13		15.22		84.78		100	
	On admission to hospital		9.71 ± 1.15		1.69 ± 0.71		0.28 ± 0.19		1.02 ± 0.28		0.21 ± 0.11		77.69 ± 9.36	
	No. in 2 months of treatment	n	46		17		29		26		20		46	
		%	100		36.96		63.04		56.52		43.48		100	
	In 2 months of treatment		11.25 ± 1.48		1.94 ± 0.61		0.36 ± 0.23		1.24 ± 0.18		0.16 ± 0.15		80.13 ± 9.72	
Group 2	No. on admission	n	46	–	6	p = 0.7491	40	p = 0.7491	10	p = 0.4514	36	p = 0.4514	46	–
		%	100		13.04		86.96		21.74		78.26		100	
	On admission to hospital		10.13 ± 1.79	p = 0.8439	1.58 ± 0.61	p = 0.9081	0.36 ± 0.14	p = 0.5711	1.08 ± 0.21	p = 0.8629	0.20 ± 0.10	p = 0.6824	74.51 ± 8.01	p = 0.7969
	No. in 2 months of treatment	n	46	–	8	p = 0.0333	38	p = 0.0333	13	p = 0.0460	33	p = 0.0460	46	–
		%	100		17.39		82.61		28.26		71.74		100	
	In 2 months of treatment		10.07 ± 1.21	p = 0.5383	1.81 ± 0.39	p = 0.8906	0.42 ± 0.22	p = 0.8667	1.09 ± 0.25	p = 0.6291	0.24 ± 0.16	p = 0.0769	79.58 ± 8.19	p = 0.9656

#the p-value is difference between parameters in Groups 1 and 2; ALT: alanine transaminase; AST = aspartate transaminase

Table 4. Bacteriostatic blood activity relative to the strain H37Rv

Hour of study	Groups of patients	The values of bacteriostatic activity of blood											
		Small 1:2 – 1:4			Medium 1:8 – 1:16			High 1:32 – 1:512			Medium and high 1:8–1:512		
		n	%		n	%		n	%		n	%	
1	1 group n = 46	–	–	–	31	67.39	p < 0.0001	15	32.61	p < 0.0001	46	100	–
	2 group n = 46	–	–		6	13.04		40	86.96		46	100	
3	1 group n = 46	–	–	–	23	50.00	p = 0.2064	23	50.00	p = 0.2064	46	100	–
	2 group n = 46	–	–		17	36.96		29	63.04		46	100	
6	1 group n = 46 (6)	18	39.13	p = 0.5152	28	60.87	p<0.0001	–	–	–	28	60.87	p = 0.5152
	2 group n = 46 (8)	15	32.61		7	10.87		24	52.17		31	67.39	

*The difference between indicators 1 and 2 groups

two months of treatment concentration of these indicators in patients of the group 1 increased significantly due to complications related to the ATD in the liver and heart. An opposite trend was noticed in patients from the group 2, which was associated with i.v. administration of ATD, both for TB and drug intoxication.

We have made researches of the drugs pharmacokinetics depending on method of their application. The choice of the examination timing was based on the pharmacodynamic properties of preparations and character of the MBT growth, the need to create high peak concentrations in the blood and hence the corresponding values of the BBA for successful treatment of TB patients.

Thus, in the 1st hour of the research, average and high BBA values in 100% of the cases among the groups were determined. In the 2nd group, the high BBA values in the 1st hour of the research were significantly higher in comparison with the control group (p < 0.05).

In the 3rd hour after the application of drugs, the BBA level was recalculated. It should be noted that although the consolidated figures for the mean and high values of BBA in the 1st and 2nd groups were observed in 100% of cases, the number of patients with high BBA level prevailed in the 2nd group, where intravenous administration of drugs was applied.

In the 6th hour of the research, the data of the 1st and 2nd groups were characterized by a further decrease of the bacteriostatic blood activity and its detection at low levels. In the group where patients received oral chemotherapy, the high BBA levels were not detected in any case. Intravenous use of ATD was slightly lower taking into consideration the consolidated figures of mean and high BBA levels compared to the group where ATD was taken orally, but this group was characterized by determination of high BBA levels in contrast to the first group where high BBAs were not detected (Table 4).

One of the most important criterion for characterizing the treatment efficacy of patients with pulmonary TB is the frequency of abacillation in patients (Tables 5, 6). According to the presented data, the frequency of observed abacillation using both microscopic and culture methods was significantly more real in the group 2 than in the 1st one.

In addition, another important criterion characterizing the treatment effectiveness of patients with pulmonary TB is healing of the destructions and disappearance of infiltrative changes (Table 7). Throughout the period of observation, the healing of destructions of lung tissue was recorded more often among the patients from the second group than in the first one.

Regarding the terms of disappearance of infiltrative changes (Table 7), so far all the observed groups were consistent with the terms of destructions healing. The only exceptions are the rare cases where infiltration had disappeared before the destruction healing occurred, or vice versa,

Table 5. **Indicators of acid-fast bacilli excretion cessation as evidenced by microscopic examination of sputum and bronchial washing**

Stages of treatment (months)	Group 1		Group 2		p-value
	n	%	n	%	
On admission to hospital	39	84.78	41	89.13	0.5365
1	18	46.15	29	70.73*	0.0238
2	12	30.77	10	24.39	0.5238
3	5	12.82	2	4.88	0.2078
5	4	10.26	0	0	–

* the p-value is difference between parameters in Groups 1 and 2

Table 6. **Indicators of acid-fast bacilli excretion cessation as evidenced by bacteriologic examination of sputum and bronchial washing**

Stages of treatment (months)*	Group 1		Group 2		p-value
	n	%	n	%	
2	25	54.35	37	80.43*	0.0066
5	19	41.30	8	17.39*	0.0106

* the p-value is difference between parameters in Groups 1 and 2

Table 7. Indicators of destruction lesion healing and infiltrative change alleviation in pulmonary tissue.

Stages of treatment (months)*	Group 1		Group 2		p-value
	n	%	n	%	
2	18	39.13	29	63.04*	0.0204
4	28	60.87	38	82.61*	0.0192
Total to 6	36	78.26	41	89.13	0.1570

a Index value at each stage is calculated based on previous values
* the p value is difference between parameters in Groups 1 and 2

when infiltration of the lung continued for some time at a time of healing.

Thus, the healing timeframes of destructions of patients from the group 2 were significantly shorter than those from the group 1. This may be related to a more massive concentration of i.v. chemotherapy at the beginning of treatment followed by penetration of ATD into the abnormal focus earlier than at oral application.

The immediate effectiveness of treatment would be covered incompletely, if the nature of residual changes after completion of the main course of antimycobacterial therapy in both groups was not assessed.

When using i.v. chemotherapy in patients with pulmonary TB, there are less residual changes observed: small residual changes at the cavern site which were healed, or absence of even minimal radiological changes stated in 29 (63.04%) patients versus 18 (39.13%) in the group 1 (p = 0.0158), and large residual changes accordingly in 17 (36.96%) and 28 (60.87%) (p = 0.0204).

Discussion

TB is out of control in developing countries due to increasing poverty, drug-resistant TB and HIV coinfection [1, 2]. The use of tablet forms of ATD does not always ensure the patient's recovery. This may have many causes, such as comorbidities, the presence of malabsorption syndrome and others, which translates to a re-

duced concentration of ATD in the blood [3, 19]. In view of such situation, it is clear that safer and better therapies of TB patients are needed. The results of this randomized study in a representative population of TB patients indicates that the first line intravenous ATD have produced faster clearance of *M. tuberculosis* and healing destruction in the lungs at a significantly higher rate than in the control arm. This response rate, which occurred within such a short period of time, has rarely been seen in oral chemotherapy trials [8, 28].

It is well known that cough, pain in the chest, increased body temperature, fever, profuse night sweats, fatigue, dyspnea, and loss of weight and decreased appetite content are requisite parameters to gauge the severity of TB [26–28]. The return of these indices to normal is the symptom of disease control and a good correlation with sputum conversion have been found [5]. Caseous pneumonia, tuberculous meningitis, disseminated and miliary TB are independent risk factors associated with poor prognosis; intravenous ATD are known to reduce mortality among these TB patients [16, 21]. Intravenous ATD helps to reduce symptoms of intoxication in a higher proportion of patients, in other words, 61.2 versus 24.9 % in control group — a ratio that matches sputum conversion rate. Consumption is a term historically synonymous with TB and represents poorly manageable wasting syndrome associated with malnutrition and chronic inflammation [29]. Finally, as judged by ALT and AST assays, intravenous ATD counteract drug-induced hepatotoxicity — an important factor that affects negatively compliance and success of TB chemotherapy.

What is the mechanism of intravenous ATD action? In each form of TB, immunopathological inflammation caused by the violation of microcirculation and trophic factors of lung tissue occurs, which may be complicated by its melting, secreting of caseating masses through the bronchi, and the formation of destructions (i.e., the process transition in the destructive form). This worsens the course of TB, resulting in the subsequent loss of a part or even the whole organ. All this complicates the penetration of oral ATD in the focus of tuberculous inflammation [4, 30]. Intravenous chemotherapy increases the concentration of ATD in the blood in a short period of time, ensures a rapid access of these drugs to the focus of tuberculous inflammation and the use of solutions of intravenous ATD provides faster detoxication in patients with TB [15, 22]. In addition, the results of studies during the past years

have proved that the antimicrobial effect of ATD depends only on their maximum concentration in the blood, whereas the duration of contact with MBT is not significant [10, 25]. We demonstrated that intravenous administration of ATD allows creating a high level of bacteriostatic blood activity and maximum concentration in blood serum of patients as much as 2.5 times higher compared to oral use.

It should be mentioned that the treatment of patients with pulmonary TB with the use of i.v. chemotherapy accelerates normalization of TB clinical aspects and the progress of a specific process. No serious adverse events including severe allergic and toxic reactions to applied i.v. chemotherapy were observed. It was found that i.v. chemotherapy has been well tolerated and safe. Thanks to i.v. chemotherapy, the terms of abacillation and the frequency of destruction healing increased together with the frequency of achievement of complete clinical and radiological cure of patients with a decrease in the number of large residual changes after the treatment. In addition, due to the use of i.v. chemotherapy, more rapid penetration of drugs into specific focus of inflammation has been achieved, full bioavailability of drugs and a 100% controllability of treatment has been observed.

This treatment effect will help to improve further patient's life after recovery of TB, prevent patient from disability due to TB and relapse of TB as well as development of drug resistance resistance of MTB [14], which in turn will reduce the costs of treatment of TB patients in the future.

Thus, the feasibility of i.v. chemotherapy for patients with pulmonary TB has been confirmed.

Conclusions

Thanks to i.v. chemotherapy, in patients with pulmonary TB, clinical aspects were eliminated faster, severe side effects of ATD have not been noticed, time of bacterial clearance and healing destruction is reduced, and the healing frequency of destructions is increased and the residual changes have been lessened.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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