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STANDARD TREATMENT REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS – ANALYSIS OF EFFECTIVENESS

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Introduction

In recent years, all over the world number of patients with multidrug-resistant tuberculosis is increasing. Ukraine was not exception [1]. Treatment of such patients in our country before 2008 was carried out empirically with present drugs, often these were only first-line drugs. This situation led to the aggravation of problem of multidrug-resistant tuberculosis (MDRTB) and a significant increase in the number of patients with this pathology. Since 2008, Ukraine introduced standardized protocols for TB care, and particular for MRTB [2, 3]. They provided uniform standard treatment regimens for all patients, using only those drugs for which the sensitivity was maintained [4]. Such an approach to the treatment of MDRTB had a positive effect and led to stabilization of TB epidemiological situation, and in recent years it led to reduce of morbidity of this disease [5]. However MDRTB incidence remains high, and that is of particular concern, a growing number of patients MDRTB among people with newly diagnosed TB [6, 7]. Therefore the search for the most effective MDRTB treatment is a priority that must be addressed to the medical community, as effective treatment for such patients is one of the main obstacles to the spread of the disease in population.

The **aim** of our study was to analyze effectiveness of different standard regimens that have been used over the years in patients with newly diagnosed pulmonary MDRTB.

Materials and methods

We analyzed 68 case histories of patients with newly diagnosed pulmonary MDRTB who were treated in Kharkiv regional TB dispensary №1 in the period from 2009 to 2014 and received TB treatment according to the clinical protocols of medical care for patients with chemoresistant tuberculosis (CRTB), which were used at that time. All patients were older than 18 years. Patients aged 18-24 years were 12 persons (17.6%); 25-34 years - 23 (33.9%); 35-44 years - 16 (23.5%); 45-54 years - 10 (14.7%); 55-64 - 4 (5.9%); and over 65 years old - 3 (4.4%). Of these, women - 14 persons (20.6%), men - 54 (79.4%).

All patients were divided into two groups. Group I included 49 patients who were treated according to Order of Ministry of Health of Ukraine № 600 from 22.10.2008, the " Standard of care for patients with chemoresistant tuberculosis". Among this group of patients, women accounted for 22.5% (11 people), men - 77.5% (38 people). By the age patients were diveded as follows: 10 patients (20.4%) were persons from 18 to 24 years; 15 patients (30.6%) - 25-34 years; 12 patients (24.5%) - 35-44 years; 8 patients (16.3%) - 45 to 54 years; another 2 patients (4%) were classified in the group of 55-64 years and 65 years. Patients in this group received the following standard scheme of therapy: 6EZAm(Km)QEt(Pt) / 12-18EZQEt(Pt); 6EZAm(Km)QPAS / 12-18EZQPAS (where E - ethambutol, Z - pyrazinamide, Am - amikacin, Km - kanamycin, Q - fluoroquinolone III-IV generation, Et - ethionamide, Pt - protionamid, PAS -paraaminosaliylic acid).

In addition, for19 patients (38.8%) of Group I in the treatment regimen was included isoniazid (H). Thus, in the group I were allocated subgroup Ia (using H) - 19 people, and Ib (without H) - 30 people, and we analyzed the efficacy of treatment in them.

Another 19 people (group II) were treated by the order of Ministry of Health of Ukraine № 1091 from 21.12.2012 "Adoption and implementation of medical and technological documents for standardization of care in tuberculosis" with scheme 8ZKm(Am)LfxPt(Et)Cs(Tz,PAS) / 12ZLfxPt(Et)Cs(Tz,PAS), where Lfx - levofloxacin, Cs - cycloserine, Tz - terizidone. There were 84.2% (16 people) of men and 15.8% (3 people) of women. Persons aged 18-24 years were 2 people (10.5%), 25-34 years - 8 people (42.1%), 35-44 - 4 people (21%), 45-54 years - 2 people (10.5%), 55-64 years - 2 people (10.5%), 1 person (5.2%) was older than 65 years. Error of proportion Δ was calculated using the formula: $\Delta = \sqrt{n1/n(1-n1/n)/n} \cdot 100\%$, where n – sample size, n1 – number of of patients with studied feature.

All patients were examined for clinical (fever, cough, body mass deficit (LBW)), X-ray (the presence of destruction in the lungs, X-ray dynamics) and bacteriological (identification of the causative agent by smear (smear microscopy by Ziehl-Nielsen) and by culture on solid and / or liquid culture media) signs of pulmonary tuberculosis in the terms provided by calendar of treatment outcomes monitoring, namely at 2 and 6 months from the start of chemotherapy (CT).

Results

At the time of MDRTB diagnosing, in patients from groups I and II, the major clinical, radiological and microbiological parameters were investigated (Table 1).

Table 1. Comparative characteristics of patients at the moment of multidrug-resistant tuberculosis diagnosing.

Figure	Group I (n=49)		Group II (n=19)	
	abs	%	abs	%
Men	38	77,5	16	84,2
Women	11	22,5	3	15,8
Mean age	36,6±4,2		37,8±5,7	

Destruction	43	87,6	15	78,9
MBT+ in smear	35	71,4	11	57,9
MBT+ in culture	45	91,8	18	94,4
Cough	36	73,5	9	47,7
Fever	24	49	13	68,4
Loss of body weight	11	22,4	5	26,3

As we can see from Table 1, patients in the compared groups were divided approximately equally. The differences in the clinical characteristics of patients from various groups depended on the timing of setting MDRTB diagnosis. On average, in group I it was 7.4 weeks, and in the group II - 5 weeks, which was due to the introduction in 2009-2012 in Kharkiv region of modern diagnostic methods for MDRTB such as BACTEC MGIT 960, GeneXpert MBT / RIF, which have significantly reduced the time of diagnosis.

Table 2. Criteria of treatment efficiency in patients with MDRTB according to standard regimens

Criteria of treatment efficiency	**Dynamics, %**	**Group**	**Time of monitoring**					
			start		**2 months**		**6 months**	
			abs	%	abs	%	abs	%
Fever	↓45±7,1	I(n=49)	24	49	11	22,5±6	2	4±2,8
	↓63,2±11,1	II(n=19)	13	68,4	7	36,8±11,1	1	5,2±5,1
Cough	↓28,6±6,5	I(n=49)	36	73,5	35	71,4±6,5	22	44,9±7,1
	↓31,6±10,7	II(n=19)	9	47,7	7	36,8±11,1	3	15,8±8,4
Loss of body weight	↓10,2±4,3	I(n=49)	11	22,4	9	18,4±5,5	6	12,2±4,7
	Без	II(n=19)	5	26,3	5	26,3±10,1	5	26,3±10,1
X-ray dynamics		I(n=49)			36	73,5±6,3	38	77,5±6
		II(n=19)			16	84,2±8,4	11	57,9±11,3
Destruction	↓20,4±5,8	I(n=49)	42	87,7	40	81,6±5,5	33	67,3±6,7
	↓31,5±10,7	II(n=19)	15	78,9	14	73,7±10,1	9	47,4±11,5
Smear +	↓67,4±6,7	I(n=49)	35	71,4	12	24,5±6,1	2	4±2,8
	↓47,4±11,5	II(n=19)	11	57,9	5	26,3±10,1	2	10,5±7
Culture +	↓77,5±6	I(n=49)	45	91,8	31	63,3±6,9	7	14,3±5
	↓78,7±9,4	II(n=19)	18	94,4	8	42,1±11,3	3	15,7±8,4

According to data of Table 2 we can see that in terms of monitoring the effectiveness of treatment in patients from group II compared with the patients of group I, marked a pronounced positive trend on criteria such as cough (after 6 months of treatment, 15.8% and 44.9% respectively), presence of destruction (after 6 months of treatment 47.4% and 67.3% respectively) indicating that the healing of cavities was more in patients from group II. Greater number of bacterioexcretion at 6 months of treatment in group II indicates better diagnosis of MDRTB pathogen.

Table 3. Effectiveness of different treatment regimens in patients with MDRTB

Treatment result	Group I (n=49)		Group II(n=19)	
	abs	%	abs	%
Residual effects of tuberculosis	34	69,4±6,6	13	68,4±10,7
Died	8	16,4±5,3	2	10,5±7
Treatment failure	3	6,1±3,4	2	10,5±7
Treatment interruption	4	8,1±3,9	2	10,5±7

Effectiveness of treatment of patients in both groups was similar, but in a group of I there were by 5.9% more deaths and 4.4% less treatment failures than in group II (Table. 3). To identify possible reasons for these differences we were isolated and analyzed within the group of I subgroups Ia (patients received H) and Ib (patients did not receive H).

Table 4. Criteria of efficiency MDRTB treatment of patients in the groups with isoniazid and without it.

Criteria of treatment efficiency	**Dynamics, %**	**Group**	**Time of monitoring**					
			Start		**2 months**		**6 months**	
			abs	%	abs	%	abs	%
Fever	↓57,9±11,3	Ia (n=19)	11	57,9	5	26,3±10,1	0	0
	↓36,6±8,8	Ib (n=30)	13	43,3	6	20±7,3	2	6,7±4,6
Cough	↓21±9.3	Ia (n=19)	13	68,4	13	68,4±10,7	9	47,4±11,5
	↓33,4±8,6	Ib (n=30)	23	76,7	22	73,3±8,1	13	43,3±9
Loss of body weight	↓10,5±7	Ia (n=19)	4	21	4	21±9,4	2	10,5±7
	↓10±5,5	Ib (n=30)	7	23,3	5	16,6±6,8	4	13,3±6,2
X-ray dynamics		Ia (n=19)			14	73,3±10,1	16	84,2±8,4
		Ib (n=30)			22	73,3±8,1	22	73,3±8,1
Destruction	↓10,5±7	Ia (n=19)	18	94,7	18	94,7±5,1	16	84,2±8,4
	↓26,7±8,1	Ib (n=30)	25	83,3	22	73,3±8,1	17	56,6±9
Smear +	↓52,7±11,5	Ia (n=19)	12	63,2	3	15,8±8,4	2	10,5±7
	↓76,7±7,7	Ib (n=30)	23	76,7	9	30±8,4	0	0
Culture +	↓68,5±10,7	Ia (n=19)	17	89,5	13	68,4±10,7	4	21±9,4
	↓83,3±6,8	Ib (n=30)	28	93,3	18	60±8,9	3	10±5,5

Analysis of the criteria of treatment effectiveness in subgroups Ia and Ib showed that in the group Ib healing of cavities was observed in more patients than in the group Ia, and destruction after 6 months of treatment was observed in 56.6% and 84.2% of patients in the subgroups, respectively. Also, in the subgroup Ib in more patients than in the subgroup Ia, at 6 months of treatment abacillation occurred (by smear (10.5% and 0%) and culturally (21% and 10%)) (Table 4).

As can be seen from Table 5, in subgroup Ib, there were significantly more deaths (18.1%) than in subgroup Ia. As can be seen from Table 5, in subgroup Ib, there were significantly more deaths (18.1%) than in subgroup Ia.

Table 5. Treatment effectiveness of patients with MDRTB in groups with isoniazid and without it.

Treatment result	Group Ia (n=19)		Group Ib (n=30)	
	Abs	%	Abs	%
Residual effects of tuberculosis	13	68,4±10,7	21	70±8,4
Died	1	5,2±5,1	7	23,3±7,7
Treatment failure	3	15,7±8,4	0	0
Treatment interruption	2	10,5±7	2	6,6±4,6

This pattern may be related to the presence in this subgroup of patients with severe concomitant diseases (HIV, endocrine pathology), which resulted in decompensation of this pathology on the background of non-effective treatment and treatment adverse reactions.

Since, for the treatment of patients with MRI under protocol No. 1091, the use of H was not provided, we compared the results of treatment of patients from group II and subgroup Ib.

Table 6. Criteria of treatment effectiveness in patients with MDRTB.

Criteria of treatment effectiveness	Dynamics for 6 months, %	Group	Time of monitoring					
			Start		2 months		6 months	
			abs	%	abs	%	abs	%
Fever	↓36,6	Ib (n= 30)	13	43,3 (±9)	6	20 (±7,7)	2	6,7 (±4,6)
	↓63,2	II (n=19)	13	68,4 (±10,7)	7	36,8 (±11,1)	1	5,2 (±5,1)
Cough	↓33,4	Ib (n=30)	23	76,7 (±7,7)	22	73,3 (±8)	13	43,3 (±9)
	↓31,6	II (n=19)	9	47,7 (±11,5)	7	36,8 (±11)	3	15,8 (±8,4)
Loss of body weight	↓9,9	Ib (n=30)	7	23,2 (±7,7)	5	16,6 (±6,8)	4	13,3 (±6,2)
	-	II (n=19)	5	26,3 (±10)	5	26,3 (±10)	5	26,3 (±10)
X-ray dynamics		Ib (n=30)			22	73,3 (±8,1)	22	73,3 (±8,1)
		II (n=19)			16	84,2 (±8,4)	11	57,9 (±11,3)
Destruction	↓26,7	Ib (n=30)	25	83,3 (±8,8)	22	73,3 (±8,1)	17	56,6 (±9)
	↓31,5	II (n=19)	15	78,9 (±9,4)	14	73,7 (±10,1)	9	47,4 (±11,5)
Smear+	↓76,7	Ib (n=30)	23	76,7 (±7,7)	9	30 (±8,4)	0	0
	↓47,4	II (n=19)	11	57,9 (±11,5)	5	26,3 (±10,1)	2	10,5 (±7)
Culture+	↓83,3	Ib (n=30)	28	93,3 (±4,6)	18	60 (±8,9)	3	10 (±5,5)
	↓78,7	II (n=19)	18	94,4 (±5)	8	42,1 (±11,3)	3	15,7 (±8,4)

As can be seen from Table 6, in group II after six months of treatment coughing was observed 27.5% less than in subgroup Ib. Also, after 6 months of therapy in this group there were for 9.2% less pulmonary tissue destructions than in subgroup Ib. Moreover, at the 2nd month of treatment in the II group 10.9% more patients had positive X-ray dynamics than in subgroup 1b. Earlier abacillation (by smear and culturally) was seen in group II.

The number of patients who effectively completed their treatment in these groups were also almost identical (Table 7).

Table 7. Treatment effectiveness in patients with MDRTB

treatment outcome	Group I (n =30)		Group II (n=19)	
	abs	%	abs	%
Residual effects of tuberculosis	21	70 (±8,4)	13	68,4 (±10,7)
Died	7	23,3 (±7,7)	2	10,5 (±7)
Treatment failure	0	0	2	10,5 (±7)
Treatment interruption	2	6,7 (±4,6)	2	10,5 (±7)

Discussion

The duration of the intensive phase of treatment according to Protocol № 600, was 6 months. According to Protocol № 1091, its duration has been increased to 8 months [8, 9]. However, as we can see from the results, the number of patients who have completed the basic course of therapy with a positive result of treatment was approximately the same in all study groups. In the group of patients who were unable to complete the course of therapy effectively, dominated patients with co-morbidities and poor adherence to treatment. These findings are consistent with those of other authors [10, 11]. When analyzing the criteria of treatment effectiveness according tocalendar for monitoring the effectiveness of treatment for these patients, we observed correlation between treatment regimen, comorbidity and treatment adherence. Effectiveness was practically independent of the longer duration of intensive phase of treatment that is confirmed by several authors [12, 13].

Conclusion

Analysis of criteria of treatment efficiency of patients with MDRTB with variety of standard schemes showed that in group II applied schemes were the most effective. It should be noted that positive effect of therapy was achieved already at 6 months of treatment, despite the fact that the Protocol provided the duration of initial phase for at least 8 months. Additional use of isoniazid had no additional positive effects but in general, when comparing the effectiveness of treatment regimens with its use, patients in this group showed a positive dynamics.

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STANDARD TREATMENT REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS – ANALYSIS OF EFFECTIVENESS

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Introduction. In recent years, the number of cases of multidrug-resistant tuberculosis (MDR-TB) has been increasing in Ukraine and all over the world. The leading factor in fight against this pathology is the effective treatment of such patients. To increase the effectiveness of treatment of

patients with MRI in 2008 unified protocols for the provision of medical care to patients were introduced in Ukraine, which offered standard treatment regimens for such patients, taking into account the individual sensitivity of pathogen to antituberculous drugs. **Aim**. Analysis of effectiveness of various standard therapy regimens that were used in patients with newly diagnosed pulmonary MDR-TB. **Materials and methods**. 68 case histories of patients with newly diagnosed pulmonary MDR-TB who were treated in the Kharkov Regional TB Dispensary № 1 in 2009-2014 and received anti-tuberculosis therapy according to current clinical protocols for medical care to patients with chemoresistant TB. All patients were older than 18 years. Patients were divided into two groups. Group I included 49 people who received treatment according to the Order of Ukrainian Ministry of Health № 600 of October 22, 2008. "Standard of medical aid for patients with chemorreistant tuberculosis". Patients from this group received the following standard therapy regimen: 6EZAm(Km)QEt(Pt) / 12-18EZQEt(Pt); 6EZAm(Km)QPAS / 12-18EZQPAS. In addition, 19 patients (38.8%) in group I were treated with isoniazid (H). Thus, in group I there were 2 subgroups: subgroups Ia (with the use of H) - 19 patients and Ib (without using H) - 30 patients, and the effectiveness of treatment in them was analyzed. Another 19 people, group II, received therapy according to the Order of Ukrainian Ministry of Health № 1091 of December 21, 2012. "On approval and introduction of medical and technological documents for standardization of care in tuberculosis" according to the scheme 8ZKm(Am)LfxPt(Et)Cs(Tz,PAS) / 12ZLfxPt(Et)Cs(Tz,PAS). All patients underwent clinical tests (fever, cough, body weight deficit), x-ray (lung destruction, X-ray dynamics) and bacteriological (pathogen detection by smear and cultureon solid and/or liquid media) signs of pulmonary tuberculosis at 2 and 6 months from the beginning of chemotherapy. **Results and discussion**. After 6 months of treatment, in group II, fewer patients complained of cough (15.8% and 44.9% in groups II and I, respectively); presence of destruction was noted in 47.4% and 67.3% of patients in groups II and I, respectively, indicating healing of cavities in a larger number of patients from group II. Effectiveness of treatment of patients in both groups was almost the same (69.4% and 68.4% in group I and II, respectively), but in the group I there were by 5.9% more deaths, and treatment failure by 4.4% than in group II. To identify possible causes of such differences, we analyzed within group I of subgroups Ia and Ib. Healing of cavities was noted in larger number of patients in group Ib, because the destruction in 6 months of treatment was determined in 56.6% and 84.2% of patients from the subgroups Ib and Ia, respectively. Also, after 6 months of treatment there were more patients with bacterioexcretion detected by both smear microscopy (10.5% and 0%) and culture (21% and 10%) in subgroup Ia than in subgroup Ib, respectively. Effectiveness of treatment was almost the same (68.4% and 70%) in subgroups Ia and Ib, respectively. There were more deaths in subgroup Ib by 18.1% than in group Ia (5.2% and 23.3%, respectively). When comparing groups of patients treated without isoniazid (groups II and Ib), it was established that in group II, after six months of treatment there were by 27.5% patients with cough (15.8% and 43.3% respectively) less than in a smaller patient than in subgroup Ib; also, after 6 months of therapy in this group, there were 9.2% less patients with destruction of lung tissue (47.4% and 56.6% in groups II and Ib, respectively). In addition, at the 2nd month of treatment there was positive X-ray dynamics in more by 10.9% patients in group II than in group Ib (84.2% and 73.3%, respectively). Also, after 2 months of treatment, there were less patients with bacterial excision (detected both microscopically (26.3% and 30%, respectively), and culturally (42.1% and 60%, respectively)) in group II than in group Ib. Effectiveness of treatment of such patients was almost the same (70% and 68,4%, respectively, in groups II and Ib), but the number of deaths was higher in group Ib than in group II (23.3% and 10.5%, respectively). Also in group II there were no treatment failures. **Conclusions**. Analysis of treatment efficiency criteria for patients with MDR-TB in various standard schemes showed that in group II the schemes were most effective. It should be noted that expressed positive effect of therapy has been already was achieved at the 6th month of treatment, despite the fact that according to the protocol, duration of intensive phase was not less than 8 months. But the additional use of isoniazid had no positive effects, and in general, when comparing the effectiveness of treatment with regimens with its use, patients from this group showed the worst positive dynamics from therapy.

Keywords: Multidrug-resistant tuberculosis, treatment effectiveness, criteria of treatment effectiveness, standard treatment regimen.