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ESTABLISHING RISK GROUPS OF MULTIDRUG-RESISTANT TUBERCULOSIS AND PLANNING ITS THERAPEUTIC APPROACH

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Abstract. Patients with a failure of the first and second course of chemotherapy have a high risk of multidrug resistance tuberculosis amoung 227 persons under study (with the rate over 80 %); patients with a tuberculosis relapse – with the rate – 52,3 %, patients with interrupted treatment according to clinical category I – 43,3 %.

Key words: multidrug resistance rate of tuberculous mycobacteria, new-onset pulmonary tuberculosis, tuberculosis relapses, chemoresistance.

Introduction. An important factor of the incidence rate of tuberculosis (TB) in different countries of the world is a rapid spread of the strains of the mycobacteria of tuberculosis (MBT) resistant to antituberculous agents (ATA). Primary resistance depends directly on the rate of acquired (secondary) resistance detected: the more patients excrete resistant MBT strains the greater the likelihood for healthy persons to be infected with chemoresistant MBT strains [1, 2]. Polychemoresistance assumes important practical significance. According to WHO data about 50 million people in the world are infected with MBT strains resistant to antimycobacterial agents; annually the percentage of the emergence of new TB cases with primary medicamental resistance is on the increase [3].

At the present time the basic treatment mode of this particular cohort of patients is prolonged and intensive chemotherapy to which MBT susceptibility is preserved.

The outcome of such therapy depends on many factors – the nature and duration of the tuberculous process, the number of medications to which MBT is resistant, chemotherapeutic regimens – their intensity, optimality, tolerance and duration, the availability of necessary drugs, control and treatment and other factors.

According to international and domestic recommendations [4] pertaining to the treatment of patients with MRT of the lungs or a suspicion of it there exist several treatment regiments and a few approaches to a patient's treatment, requiring the administration of a repeated course of chemotherapy [5, 7, 8, 10]. But neither of the approaches is universal, so long as it has both advantages and disadvantages [9]. To date the best policy as to the management of patients with a repeated treatment and a high risk of multidrug-resistance has not been determined [6, 11].

First, for the reason that no groups of a high risk of multiresistance among persons with a repeated course of treatment have been established, secondly, owing to the fact that no controlled studies, dealing with an analysis of the efficacy of these approaches have been carried out, WHO is inclined to think that it is better to use standard regimens to treat patients with a repeated treatment, since owing to standardization they are less vulnerable as to the risk of further spread of multidrug-resistance [7, 8, 12].

However, these inferences are purely theoretical and are not corroborated by controlled studies. Moreover, it is necessary to elaborate a standard regimen for each country and, probably, for a region of a country on the basis of the data of epidemmonitoring of medicamental resistance of MBT [8, 9].

A need of applying standard regimens of chemotherapy in patients with a high risk of MRT is also stipulated by shortcomings of the drug MBT susceptibility testing. In order to evaluate the susceptibility of MBT to antituberculous agents (ATA) at the Chernivtsi Regional TB Dispensary the method of inoculation on the Levenstein-Jensen medium based on the technique regulated by order №45 of Ukraine's MHP of February 8, 2000 was used. The use of the routine methods of laboratory diagnostics of tuberculosis makes it possible to obtain the results of the test of MBT susceptibility to ATA in 3-3,5 months since the first examination of a patient.

Since Ukraine has no exact data, concerning the prevalence and profile of medicamental resistance of MBT a group of risk in relation to pulmonary multidrug-resistance tuberculosis of patients in whom unknown susceptibility of mycobacteria to ATA in Bucovyna must be determined on the basis of a cohort analysis of monitoring of the results of a previous course of treatment, the spread and the profile of resistance of mycobacteria of this particular cohort of patients.

Taking into account the above-mentioned, the diagnosis of multiresistant tuberculosis is made, in the first place, on the basis of the results of treatment which are confirmed by the findings of drug susceptibility and not on the contrary.

The objective of research. To study risk groups, concerning the formation of multidrug-resistant pulmonary tuberculosis and raise the efficacy of its treatment in patients in whom susceptibility of the causative agent to antituberculous agents is unknown.

Material and methods of the research. 227 previously treated patients afflicted with new-onset tuberculosis and disease relapses have been examined, using a clinical, roentgenological, clinicolaboratory, microbiological, statistical methods.

Results of the investigation and the subject under discussion. Among the persons under study (227 patients) there were 33 patients in whom a failure of the first course of chemotherapy (CT) was registered, 90 persons were with a suspended course of treatment for more than 2 months, 18 persons with a failed repeated course (there were both patients with NOTL and with recurrences) who were treated up to 10 months according to the second clinical category. 86 patients suffered from a TB relapse and who were not treated according to the second clinical category (Table 1).

In conformity with the investigations carried out on the basis of the findings of statistical factors of active NOTL with bacterioexcretion of patients who were registered at the Chernivtsi Regional TB Dispensary from 2002 to 2008 it has been established that the dynamics of general drug resistance among patients with tuberculosis detected for the first time did not change considerably, but multidrug resistance is observed in 19% of retreated patients.

Monitoring of multiresistance over the period from 2008 to 2010 has demonstrated that the dynamics of MRT in newly detected patients has not reliably changed. An essential increase of the number of patients with multidrug-resistant tuberculosis is observed among retreated cohorts which exceeded 2.8 times this index in 2010 as compared with 2008 that is indicative of insufficient efficacy of chemotherapy used in this particular cohort of patients.

It has been established that among 227 examinees the level of MBT multiresistance fluctuated from 43.3% in patients with suspended treatment to 88,8 % in patients with a failure of a repeated course of chemotherapy.

However, in order to define the degree of probability in each group of these patients we made use of the definition of the odds ratio concerning the presence of multidrug resistance in them. These findings are presented in Table 2.

A correlation between a patient's medical history relative to the previous treatment and the presence of multidrug resistance was evaluated be means of the odds ratio (OR) according to a 4-column table compiled on the principle of comparing two groups with the presence and absence of a sign that is under study. If the value of the ratio of chances for unwanted sequelae is less than 1 this is an indication of a positive effect of the factor in question directed at reducing a risk of this sequela.

With a low frequency of an event the value of the odds ratio equals approximately a relative risk. If the value of the odds ratio is more than 1, it was indicative of a high risk of the influence of the factor in question on the sign that is investigated.

Thus, with the rate of multidrug resistance in the group of 22 % previously treated patients that constituted 56,8 %, we found out that reliably vulnerable groups concerning multidrug resistance are patients with a failure of the 1st and repeated course of chemotherapy with equally high values of the odds ratio 5,5 and 6,08 ($p>0,05$) respectively. In patients with a suspended course of treatment and disease relapses there exist a relative risk of the presence of multidrug-resistance with the odds ratio – 0,58 and 0,83 respectively that does not differ considerably between themselves ($p>0,05$) however, it is reliably lower than in patients of the previous groups ($p<0,05$).

The studies presented make it possible to single out groups of patients who should not be treated ac-

Table 1

The structure of the cohort of patients with pulmonary tuberculosis who require retreatment based on the type of a case of the tuberculosis disease

The number of patients								
Total	The type of a case of the tuberculosis disease							
	Suspended treatment		Failure of the 1st course of treatment		Failure of the 2nd course of treatment		Tuberculosis relapse	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
227	90	39,6	33	14,5	18	7,9	86	37,9

Table 2

The ratio of chances as to the presence of multidrug resistance in patients with NOTL and disease recurrences, requiring the administration of retreatment

Groups of patients treated earlier	Multidrug resistance of MBT				OR (95 % CI)
	There is		There isn't		
	abs.	%	abs.	%	
Failure of the 1st course of CT	29	87,9	4	12,1	5,5 (1,87-16,18)
Suspended treatment	39	43,3	51	56,7	0,58 (0,35-0,95)
Failure of the 2nd course of CT	16	88,8	2	11,2	6,08 (1,36-27,05)
Recurrence	45	52,3	41	47,7	0,83 (0,5-1,37)
Total	129	56,8	98	43,2	

cording to category 2 with the use of the first-line medications due to a high likelihood of the presence of MBT multidrug resistance: the patients with a default of the first and a repeated course of chemotherapy (the odds ratio (OR) – 5,5 and 6,08. The patients with a suspended treatment and disease relapses have a relative risk of available MBT multidrug resistance (the odds ratio (OR) – 0,58 and 0,83).

Patients with a failure of the first and repeated CT course should be prescribed standard regimens of CT based on the 4th category in case of the absence of the test of drug susceptibility of MBT to first-line ATAs.

In patients with suspended therapy and tuberculosis recurrences preference should be given to empiric CT regimens over standard regimens based on the second clinical category so long as they include 5-7 medications with a view of preserving rather a high likelihood that tuberculosis mycobacteria will retain susceptibility at least to 4 of them.

In accordance with the findings of the research, the regimen based on the second clinical category fits to only half of the patients (47,7 %), first-line antituberculous agents being used in it.

We have carried out an analysis of the findings, dealing with MBT susceptibility to ATAs in 43 patients with NOTL with a suspicion of multidrug resistant tuberculosis and unknown susceptibility of the causative agent to antituberculous drugs (the presence of the multidrug resistance was established upon obtaining the results of MBT drug susceptibility testing).

Extensive resistance of MBT was identified in almost half of the patients (44,2 %) with MRT, except the basic antituberculosis drugs (isoniazid and rifampicin): to streptomycin – in 55,5 % of the patients, pyrazinamide – in 27,9 %, ethambutol – in 32,6 %. In other words, the administration of a repeated course to half of the patients based on the 2nd clinical category is impossible.

A relatively not high level of MBT resistance to kanamycin (K) and ethionamid (Et) – 2,3 % and 1,6 % respectively was observed among the persons under study, enabling to use these drugs in patients requiring retreatment under the standard regimens of chemotherapy according to the 4th clinical category.

We have carried out a comparative analysis of the efficiency of various regimens of chemotherapy in patients with pulmonary tuberculosis with unknown susceptibility of tuberculosis mycobacteria to antimycobacterial drugs among groups of risk of the development of multidrug resistant tuberculosis.

By the time of obtaining the test of MBT susceptibility to ATAs the findings had been analyzed: sputum conversion in 76,9 % of the cases occurred at the expense of administering the empiric regimen of chemotherapy to the patients, the treatment based on the 1st category – in 52 % of the patients, according to the 2nd category – 40 % of the cases. The cessation of bacterioexcretion based on a swab in 29 cases (67,4 %) based on a culture – 14 (32,6 %), a decrease of bacterioexcretion in 39,5 % (17 persons) of the cases. Partial resorption of focal-infiltrative changes was observed in 48,8 %, insignificant regression of caverns was marked in 39.5 % (17 patients). An abatement of clinical manifestations was established in 39,5 % of the cases (17 persons).

The efficiency of the standard and individual regimens of chemotherapy was evaluated in 6 months since the initiation of the treatment. A decrease of bacterioexcretion at this moment with the standard and individual regimens of chemotherapy occurred for certain in 15 % and 60,9 % respectively. Partial resorption of focal-infiltrative changes in

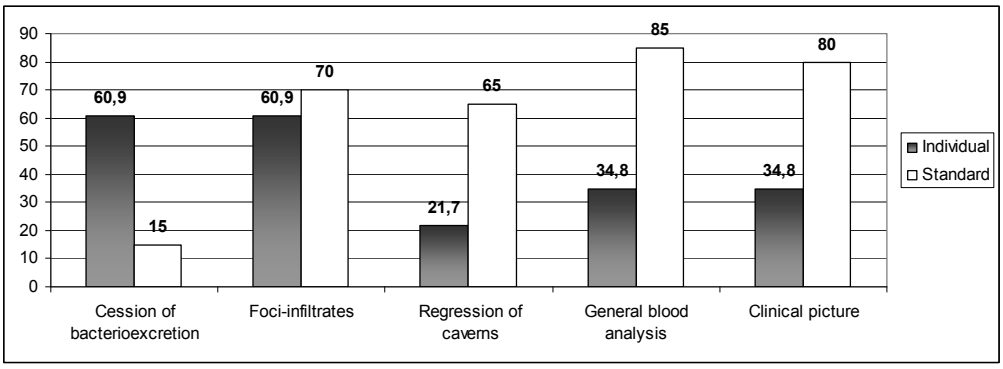

Fig 1. Efficiency of chemotherapy regimens

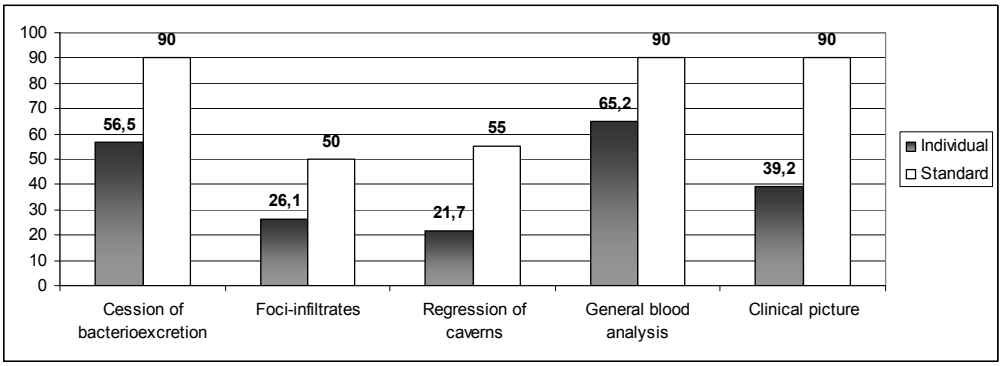

Fig. 2. Efficiency of the chemotherapeutic regimen upon discharging

70 % and 60,9 %, a regression of caverns under the existing regimens distinguished considerably, 65 % versus 21,7 % regression of caverns. Positive changes in a common blood analysis were observed in case of the standard regimen – 85 % and 34,8 % in case of the individual one, improved clinical manifestations – 80 % and 43,8 % respectively and these are illustrated in Fig. 1.

Thus, in spite of an individual selection of chemotherapy, preference was given to the standard regimen of chemotherapy ($p>0,05$).

The next evaluation of regimens was carried out on discharging the patients from the in-patient department, in 16,8±7,2 months on the average. A complete stoppage of bacteriosecretion is observed in 90 % in case of the standard regimen, whereas with the individual one – in 56,5 % of the cases. Complete resorption of focal- infiltrative changes was observed in 50 % of the patients and 26,1 % respectively. Cavernous regression with the standard regimen is seen in 55 % of the patients, whereas in case of the individual regimen – in 21,7 % of the cases. A normalization of the indices of the general blood analysis in case of the standard and individual regimens of chemotherapy was marked in 90 % and 65,2 % of the persons respectively. The absence of the basic clinical manifestations under these conditions was observed in 90 % in case of the standard regimen and 39,1 % with the individual one and is demonstrated in Fig. 2.

Thus, the most effective regimen of chemotherapy in patients with multi-drug resistant tuberculosis was the standard one.

Having analyzed the results of the treatment, it turned out that in connection with stabilization of the pulmonary process and a cessation of bacterioexcretion in patients with multi-drug resistant pulmonary tuberculosis as much as 72,1 % (31) of the patients were discharged from hospital. 19,4 % (6) out of them were readmitted in a certain period of time, taking into account periodic exacerbations of this particular disease. Two persons (4,7 %) were discharged with a postmortem epicrisis, due to a break of the hospital regimen, 23,2 % (10) of the patients were transferred to a course of aftercare under the in patients conditions of the Molodiia Interdistrict TB Dispensary.

Thus, summarizing the above stated, one can say, that recovery was observed in 55 % (11) of the cases, a stoppage of bacterioexcretion – in 35 % (7) among patients with multidrug-resistant tuberculosis of the lungs who were administered the standard regimen of chemotherapy. Recovery among persons administered the individual regimen of chemotherapy was registered in 21,7 % (5) of the persons, a stoppage of bacterioexcretion – in 34,8 % (8 patients).

The findings obtained as a result of the research carried out by the authors agree with those of other studies that point out the efficiency of the empiric regimen of chemotherapy towards the resistance of tuberculous mycobacteria at the expense of prescribing 5-7 drugs for the purpose of preserving rather a high likelihood of the fact that tuberculosis mycobacteria will retain susceptibility at least to 4 of them. Evaluating the regimens of chemotherapy on discharging from hospital, regardless of an individual selection of chemopreparations, the standard regimen turned out to be more effective (EK (Am) ZEt (Pass) Q or EZEtPASSQ) on the basis of using 2nd line medications and fluoroquinolones.

For the sake of treating patients with multidrug-resistant tuberculosis the following second-line drugs are used in Ukraine: ethionamide (prothionamide), kanamycin (amikacin), fluoroquinolones of different generations, PAS(A). Only streptomycin, ethambutol and pyrazinamide out of the first-line antituberculosis drugs are good to be used in case of the development of multidrug resistance. However, with extensive medicamental resistance, as it was established by the results of our research, all the 1st-line antituberculous drugs lose their potency. In other words, all in all, 4-7 antituberculosis drugs from all groups are available for the treatment of patients with multidrug-resistant tuberculosis.

One of the basic principles of chemotherapy of patients with multidrug- resistant tuberculosis is the use of no less than 4 antimycobacterial drugs (first, second- line and reserve ones) to which MBT are susceptible in case of their satisfactory tolerance. But under the conditions of MBT resistance up to 4 and a larger number of antituberculous drugs and in many cases, in addition, intolerance of some of them it is impossible to provide a comprehensive regimen of antituberculosis therapy or institute therapy at all.

The presence of extensive tolerance of MBT in a large enough number of patients with MRTB examined by us should be taken into account later on, when structuring empiric regimens of chemotherapy which are worth using in patients with suspended treatment and tuberculosis recurrences for the purpose of avoiding the phenomenon of induction (enhancement) of MBT resistance to a greater number of ATAs. To use instead of pyrasinamide – ethionamide/prothionamide or cycloserine, instead of ethambutol – PAS(A), instead of streptomycin – kanamycin/amikacin.

To-date, in the presence of extensive drug resistance in patients with MRTB raising the efficacy of treatment of such patients is possible by many different ways. The first one is synthesis of new antituberculous agents. But this way requires investing a lot of money and what is most important it is very prolonged. The second one is an evaluation of the antituberculosis activity of the antimycobacterial drugs of a wide spectrum of action. It is a promising trend which is being actively elaborated currently [7]. The antituberculous proprieties of fluoroquinolones, macrolides and some other compounds have already been established. The third one is the most topical in Ukraine for to-day – the registration of the second-line antituberculous agents already known and which are not produced in our country.

Conclusions

1. A very high risk of multidrug-resistant tuberculosis of the lungs is characteristic of patients with

failure of the first course of chemotherapy (87,9 %) and failure of the repeated course (88,8 %); a high risk of multidrug-resistant tuberculosis is inherent to patients with tuberculosis recurrence and suspended treatment in compliance with the 1st category (with the rate of 52,3 % and 43,3 % respectively).

2. It is advisable to prescribe standard regimens of chemotherapy based on the 4th category to patients with a failure of the first and repeated course of chemotherapy in case of the absence of the test of medical susceptibility of mycobacteria to antituberculous drugs of the first line.

3. A relatively not high level of resistance of MBT to kanamycin (K) and ethionamide (ET) – respectively 2,3 % and 1,6 % among the persons under study enables to use these drugs in patients, requiring retreatment in terms of standard regimens of chemotherapy in accordance with the 4th clinical category prior to obtaining the results of MBT drug susceptibility testing.

4. Taking into consideration the presence of extensive medicamental resistance in 44,2 % of the patients with multidrug-resistant tuberculosis in case of administering empiric regimens to patients with a tuberculosis relapse or suspended treatment preference should be given to oral antituberculosis drugs of the second-line (ehionamide, prothionamide, cycloserine, PAS(A)) with a view of avoiding the phenomenon of MBT resistance induction to a greater number of ATAs.

5. While comparing the efficacy of different regimens of chemotherapy in patients afflicted with pulmonary tuberculosis, it has been established that the most effective regimen is the empiric regimen of chemotherapy (EZS(K)PASQ or EZK(Pt/Cap)CsQ) prior to evaluating tuberculous mycobacteria resistance (the basic course), at the expense of prescribing a combination of 5-7 drugs During a stage of continuing treatment, evaluating the regimens of chemotherapy upon discharging from hospital, the standard regimen turned out to be more effective (EK(Am)ZEt (PASS)Q or EZEtPASSQ at the expense of using second-line drugs and fluoroquinolones.

Practical value of the results obtained. Risk groups in which, multidrug-resistant pulmonary tuberculosis may develop have been established. The authors have carried out an analysis of the efficacy of the most rational regiments of chemotherapy of patients with pulmonary tuberculosis with due regard for an evaluation of antimycobacterial susceptibility of the causative agent enabling to improve the results of chemotherapy of this particular category of patients and forestalling the development of multiresistant forms.

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УСТАНОВЛЕНИЕ ГРУПП РИСКА МУЛЬТИРЕЗИСТЕНТНОГО ТУБЕРКУЛЕЗА И ОПРЕДЕЛЕНИЕ ТАКТИКИ ЛЕЧЕНИЯ

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Резюме. Среди 227 исследуемых лиц высокий риск мультирезистентного туберкулеза (с частотой свыше 80 %) имеют пациенты с неудачей первого и второго курсов химиотерапии; с частотой 52,3 % – пациенты с рецидивом туберкулеза, с частотой 43,3 % – пациенты с прерванным лечением за 1 клинической категорией.

Ключевые слова: частота мультирезистентности микобактерий туберкулеза, впервые диагностированный туберкулез легких, рецидивы туберкулеза, химиорезистентность.

УСТАНОВЛЕННЯ ГРУП РИЗИКУ МУЛЬТИРЕЗИСТЕНТНОГО ТУБЕРКУЛЬОЗУ ТА ВИЗНАЧЕННЯ ТАКТИКИ ЛІКУВАННЯ

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Резюме. Серед 227 досліджуваних осіб високий ризик мультирезистентного туберкульозу (з частотою понад 80 %) мають пацієнти з невдачею першого та другого курсу хіміотерапії; з частотою 52,3 % – пацієнти з рецидивом туберкульозу, з частотою 43,3 % – пацієнти з перерваним лікуванням за 1 клінічною категорією.

Ключові слова: частота мультирезистентності мікобактерій туберкульозу, вперше діагностований туберкульоз легень, рецидиви туберкульозу, хіміорезистентність.

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