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ВЛИЯНИЕ ИНТЕРВАЛЬНЫХ ГИПОКСИЧЕСКИ-ГИПЕРОКСИЧЕСКИХ ТРЕНИРОВОК НА МАРГАНЦЕВУЮ СУПЕРОКСИДДИСМУТАЗУ МИОКАРДА КРЫС

Н.Н.Стешенко, Т.И.Древицкая, О.А.Гончар, И.Н.Маньковская

Резюме. Изучали влияние интервальных гипоксически-гипероксических тренировок (ИГГТ) на активность, экспрессию белка и мРНК Mn-супероксиддисмутазы в митохондриях миокарда крыс после влияния острой гипоксии. Показано, что использование ИГГТ приводит к снижению гиперактивации Mn-СОД и индуцирует экспрессию белка данного антиоксидантного фермента в митохондриях миокарда после действия острой гипоксии.

Ключевые слова: гипоксия, гипероксия, митохондрии, Mn-супероксиддисмутаза.

THE INFLUENCE OF INTERMITTENT HYPOXIA/HYPEROXIA TRAININGS ON THE RAT MYOCARDIAL SUPEROXIDE DISMUTASE

M.M.Steshenko, T.I.Drevytska, O.O.Honchar, I.M.Man'kovs'ka

Abstract. The influence of intermittent hypoxic-hyperoxic trainings (IHHTS) on the activity, expression of protein and mRNA of Mn-superoxide dismutase in myocardial mitochondrias of rats has been studied after the influence of acute hypoxia. It has been shown that the use of IHHTS results in a lowered hyperactivation of Mn-SOD and an enhancement of the protein expression of this particular enzyme in myocardial mitochondrias after the action of acute hypoxia.

Key words: hypoxia, hyperoxia, mitochondria, Mn-superoxide dismutase.

O.O.Bogomolets' Institute of Physiology of Ukraine's NAS (Kyiv)

Рецензент – проф. Ю.Є.Роговий

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[1]L.D.Todoriko, [1]A.V.Boiko, [1]I.V.Yeremenchuk, [2]U.M.Lesuk

ANALYSIS OF THE EFFICACY OF CHEMOTHERAPY OF MULTIDRUG-RESISTANT TUBERCULOSIS UNDER THE CONDITIONS OF THE SPREAD HIV/AIDS EPIDEMIC

[1]Bukovinian State Medical University, City of Chernivtsi
[2]Chernivtsi Regional Prevention Center for AIDS

Abstract. The authors have carried out an analysis of the efficacy of the most rational regimens 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 and forestalling the development of multiresistant forms, iincluding in HIV-infected persons.

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

Introduction. The tuberculosis (TB) epidemic is on the rise in many countries, including Ukraine. If left untreated the active form of TB will kill two of every three people.

An important factor of the incidence rate of tuberculosis is a rapid spread of the strains of the mycobacteria of tuberculosis (MBT) resistant to antituberculous agents (ATA). This problem is further compounded by HIV coinfection, since one-third of AIDS-related deaths results from TB. Ukraine has the highest prevalence of TB/HIV co-infection in Eastern Europe (van der Werf et al. 2006). Multidrug-resistant tuberculosis has emerged as a global epidemic, with 425,000 new cases estimated to occur annually. The global human immunodeficiency virus (HIV) infection epidemic has caused explosive increases in TB incidence and may be contributing to increases in multidrug-resistant tuberculosis prevalence.

Institutional outbreaks of MDR-TB have primarily affected HIV-infected persons. A delayed diagnosis, inadequate initial treatment and prolonged infectiousness led to extraordinary attack rates and case-fatality rates among HIV-infected persons. Whether this sequence occurs in communities is less clear. Multidrug-resistant tuberculosis appears not to cause infection or disease more readily than drug-susceptible TB in HIV-infected persons. HIV infection may lead to a malabsorption of anti-TB drugs and acquired resistance. HIV-infected patients with multidrug-resistant tuberculosis have unacceptably high mortality; both antiretroviral and antimycobacterial treatments are necessary [9].

The treatment of the multidrug-resistant forms of pulmonary tuberculosis characterized by a rapid MBT propagation, massive infiltrative-caseous changes in the lungs, numerous destructions of the pulmonary tissue, pronounced intoxication syndrome, encounters considerable difficulties. Intensive chemotherapy with the use of ATA of the 1st and 2nd lines is not always effective, disease progression often against a background of therapy, resulting in fatal outcomes. The treatment of such forms is considerably complicated due to an insufficient amount of second-line antituberculous agents in case of extensive MBT resistance, their poor tolerance and a high cost of therapeutic regiments [4]. The principal cause of a low efficacy of treatment of patients afflicted with MBT is the insufficient efficacy of the medications of the 2nd line as compared with isoniazid and rifampicin, acting bactericidally on MBT. All the second-line antituberculous agents (except fluoroqiuonolones) act on the MBT bacteriostatically, their minimal inhibiting concentration in relation to mycobacteria is essentially lower (10-20 times) than that of isoniazid and rifampicin [5].

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 [3] pertaining to the treatment of patients with MRT of the lungs or a suspicion of it there exist several treatment regimens and a few approaches to a patient's treatment, requiring the administration of a repeated course of chemotherapy [4, 6, 8]. But neither of the approaches is universal, so long as it has both advantages and disadvantages [7]. 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 [5].

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, clinico-laboratory, 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).

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 by means of the odds ratio (OR) according to a 4-column table complied 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.

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 dis-

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	

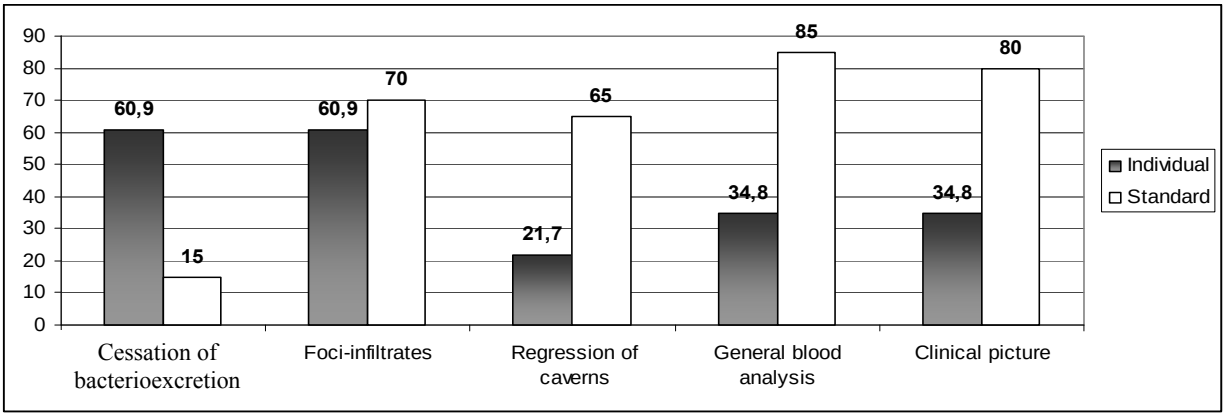

Fig. 1. Efficiency of chemotherapy regimens

ease 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).

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. The efficiency of the standard and individual regimens of chemiotherapy was evaluated in 6 months since the initiation of treatment.

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.

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

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)

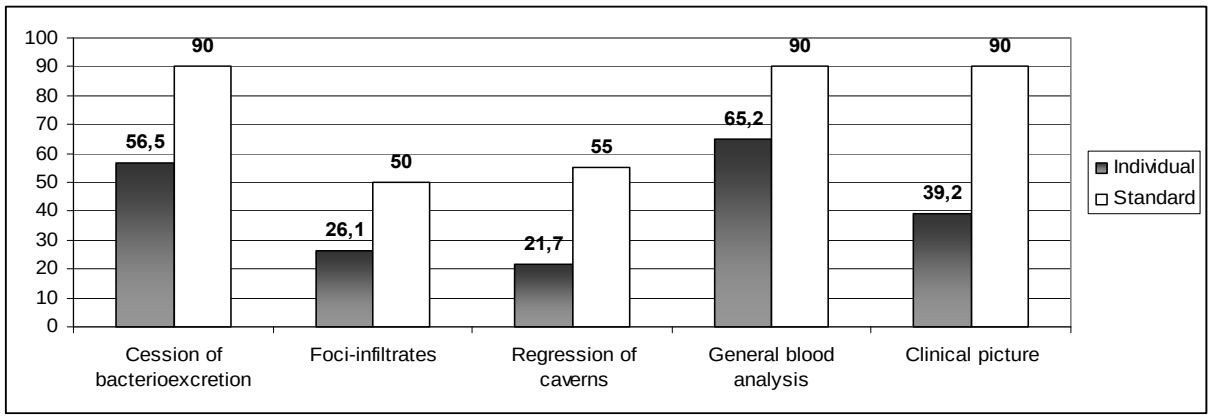

Fig. 2. Efficiency of the chemotherapeutic regimen upon discharging from hospital

ZEt (Pass) Q or EZEtPASSQ) on the basis of using 2nd line medications and fluoroquinolones.

Conclusions

1. A very high risk of multidrug-resistant tuberculosis of the lungs is characteristic of patients with a failure of the first course of chemotherapy (87,9 %) and a 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. 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.

4. The 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 and forestalling the development of multiresistant forms at HIV-infected persons.

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АНАЛИЗ ЭФФЕКТИВНОСТИ ХИМИОТЕРАПИИ МУЛЬТИРЕЗИСТЕНТНОГО ТУБЕРКУЛЕЗА В УСЛОВИЯХ РАСПРОСТРАНЕНИЯ ЭПИДЕМИИ ВИЧ/СПИДА

Л.Д.Тодорико, А.В.Бойко, И.В.Еременчук, Ю.М.Лесюк

Резюме. Проведен анализ эффективности наиболее рациональных режимов химиотерапии больных туберкулезом легких с учетом оценки антимикобактериальной чувствительности возбудителя, что дает возможность улуч-

шить результаты химиотерапии и предупредить развитие мультирезистентных форм, в том числе у ВИЧ-инфицированных пациентов.

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

АНАЛІЗ ЕФЕКТИВНОСТІ ХІМІОТЕРАПІЇ МУЛЬТИРЕЗИСТЕНТНОГО ТУБЕРКУЛЬОЗУ В УМОВАХ ПОШИРЕННЯ ЕПІДЕМІЇ ВІЛ/СНІДУ

Л.Д.Тодоріко, А.В.Бойко, І.В.Єременчук, Ю.М.Лесюк

Резюме. Проведено аналіз ефективності найбільш раціональних режимів хіміотерапії хворих на туберкульоз легень з урахуванням оцінки антимікобактеріальної чутливості збудника, що дає можливість покращати результати хіміотерапії та запобігти розвитку мультирезистентних форм, у тому числі, у ВІЛ-інфікованих пацієнтів.

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

Буковинський державний медичний університет, м. Чернівці
Чернівецький обласний центр профілактики та боротьби зі СНІДом

Рецензент – проф. О.І.Федів

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[1]Л.Д.Тодоріко, [1]В.О.Степаненко, [2]О.С.Шевченко, [1]А.О.Герман, [1]Б.І.Квасницький

РОЛЬ ПАТОГЕНЕТИЧНОЇ ТЕРАПІЇ В ЛІКУВАННІ ХВОРИХ НА ХІМІОРЕЗИСТЕНТНИЙ ТУБЕРКУЛЬОЗ

[1]Буковинський державний медичний університет, м. Чернівці
[2]Харківський національний медичний університет

Резюме. Патогенетична терапія, спрямована на підвищення імунітету, опірності імунітету до туберкульозної інфекції, є обов'язковим компонентом лікування хворих на хіміорезистентний туберкульоз легень.

Ключові слова: хіміорезистентний туберкульоз, лікування, патогенетичні засоби.

Проблема фармакотерапії туберкульозу стала на сьогодні пріоритетним питанням у зв'язку з недостатньою ефективністю методів традиційної терапії, спрямованої на пригнічення бактеріальної популяції. Це пов'язано, перш за все, із збільшенням відсотка пацієнтів із множинною медикаментозною стійкістю до антимікобактеріальних препаратів (АМБП) та поєднанням із ВІЛ-інфекцією – захворюванням, що розвивається в результаті тривалого персистування вірусу імунодефіциту людини (ВІЛ) у лімфоцитах, макрофагах та клітинах нервової системи і характеризується прогресуючою деструкцією імунної системи [8].

Патогенетична терапія, спрямована на підвищення імунітету, опірності організму до туберкульозної інфекції, є обов'язковим компонентом комплексного лікування хворих на туберкульоз.

Формуванню мікобактерій туберкульозу (МБТ), резистентних до хіміопрепаратів, сприяє, насамперед, пригніченню клітинного імунітету, яке вперше виникає під впливом факторів ризику і в подальшому спричиняє розвиток туберкульозу в інфікованої людини.

Клінічні прояви туберкульозу легень, його перебіг та результати лікування тісно пов'язані з неспецифічною реактивністю хворого, його компенсаторними можливостями, станом імунної системи, особливо за наявності множинної резистентності МБТ до АМБП [8].

Відомо, що у хворих на вперше діагностований туберкульоз, спричинений поліхіміорезистентними МБТ, відмічається порушення балансу між оксидантними та прооксидантними властивостями крові, що проявляється підвищенням у сироватці крові вмісту продуктів ліпопероксидації на тлі зниження активності ферментів системи антиоксидантного захисту [2].

У хворих на туберкульоз легень із порушеннями метаболічного гомеостазу успішно застосовується Флуімуцил – антибіотик ІТ та Тимоген. Флуімуцил – антибіотик ІТ – це лікарський засіб, до складу якого входять N–ацетилцистеїн та тіам-