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I.O. Semianiv

Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi

REATMENT OF PATIENTS SUFFERING FROM PULMONARY TUBERCULOSIS WITH CONCOMITANT DAMAGES OF HEPATO-PANCREATO-BILIARY SYSTEM TAKING INTO ACCOUNT DELETION POLYMORPHISM OF XENOBIOTICS DETOXICATION SYSTEM GENES OF GLUTATHIONE-S-TRANSFERASE

Keywords: *tuberculosis, GST, comorbidities, treatment, injected drugs.*

Abstract. *Assessing the differences between the clinical and laboratory tolerance of tubrculosis drugs according to the way of administration, it was proved the importance of individualization of the standard treatment at patients with hepatobiliary and pancreatic disorders and polimorphysm of glutathione-S -transferase (GST).*

Introduction

According to the World Health Organization (WHO) Treatment Guidelines anti-TB drugs are classified into five groups, based on evidence of efficacy, potency and drug class. In the frame of actual used DOTS (Directly Observed Treatment Short Course Chemotherapy) strategy [5], the anti-TB treatment is standardized, meaning that all patients receive the same regimens, they being included in well defined groups. The standard treatment has advantages over individualized treatment by preventing prescription errors, appropriate appreciation of drug needs, distribution and monitoring [3]. By economical mean, standard treatment shows reduced costs and permits a comparable evaluation of treatment outcomes [3].

Clinical monitoring of the treatment is essential for recognizing adverse drug effects [4]. Minor side effects (jaundice, nausea, vomiting) permit the continuation of TB treatment with an associated symptomatic treatment. If the patient develops a major side-effect, the responsible drug is stopped and the patient is referred to a specialized health care facility for further management [2].

Some of the genes, the expression of which plays a key role in the resistance of cells to the effects of free radicals by lipid peroxidation and oxidative modification of proteins, preventing breakage of DNA, biosynthesis of prostaglandins, transportation and metabolism of bilirubin, hormones are genes which code the synthesis of glutathione-S-transferase (GST) [6]. GST are enzymes of the second phase of detoxification systems which protect the body against endogenous oxidative stress and exogenous toxins, catalyzing conjugation of sulfhydryl groups of reduced glutathione and rendering harmless various electrophilic compounds, including products of lipid and DNA oxidation [6].

The aim of the study was to evaluate the effectiveness of treatment by means of injectable forms of isoniazid and rifampicin in patients with concomitant lesions of hepato-pancreato-biliary system considering the polymorphism of the gene glutathione-S-transferase.

Material and methods

A prospective, descriptive, case-control study was realized including 60 new pulmonary infiltrative drug-susceptible cases, with hepatobiliary and pancreatic comorbidities. The study was performed during the period 1.1.2013 - 1.1.2014. Patients were hospitalized in the Chernivtsi Regional Clinical Phtysiopneumological Dispensary. All selected patients were microscopically positive for acid fast bacilli and were treated according to the established new case category. Patients were distributed in a study group, consisting of 30 patients treated with oral forms of isoniasid and rifampicin and haplotypes (GSTM1+ / GSTT1 0/0, GSTT1+ / GSTM1 0/0, GSTT1 0/0 / GSTM1 0/0), and the control group, consisting of 30 patients treated with injectable forms of anti-TB drugs and had haplotypes (isoniasid and rifampicin) and haplotypes (GSTM1+ / GSTT1 0/0, GSTT1+ / GSTM1 0/0, GSTT1 0/0 / GSTM1 0/0). Pyrazinamide and ethambutol were used in oral form. First-line injected drugs were rifampicin (Ріфонат, "Юрія-Фарм" [Rifonat, "Uriya-Pharm"], Ukraine) 30 mg/ml (600 mg) solved in 100 ml of physiological solution of NaCl and was injected intravenously; isoniasid (Бітуб, "Юрія-Фарм", [Bitub, "Uriya-Pharm"], Ukraine) 100 mg/ml (300 mg) solved in 100 ml of physiological solution of NaCl and was injected intravenously. General established results:men vs women rate was 3/1, with predominance of men in both

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groups and a medium age of patients was established 39,6 ± 1,3 years old in SG and 38,7± 1,6 years old in CG. So, according to the age and sex distribution, the patients were similar distributed, that permitted a comparable assessment of selected groups. Hepatobiliary and pancreatic disorders were diagnosed using abdominal echography and liver functional tests: serum albumin, bilirubin (direct and indirect), transaminases (ALT, AST), serum creatinine and urea, timol test.

Results and discussion

Clinical efficacy of injected/oral forms of the first line anti-TB drugs HIN and RIF was assessed after 2 months of treatment according special developed symptomatology scale of intoxication syndrome (asthenia, anorexia, loss of weight, underweight/cachexia, fever/subfebril temperature, night sweets) and bronchopulmonary scale (cough, expectorations, hemoptysis, dyspneea grade according MRC scale, thoracic pain). The clinical expressiveness was distributed in levels: high, moderate, low and light. It was established that clinical state evaluated through intoxication symptomatology of the patients with pulmonary TB and hepatobiliary/pancreatic comorbidities at the end of intensive phase was better in CG than in SG.

Radiological dynamics under the influence of different forms of anti-TB drugs and duration (60, 90, 120 days of intensive phase) showed a more evident difference between groups of patients. So, the injected first-line drugs (RIF and HIN) established a positive dynamics (resorbtion of parenchimal infiltrates, reduction of lung tissue destructions) in CG than in SG after 2 and 3 months of the treatment.

Microbiological assessment, through smear microscopy is essential tool for the treatment monitoring according to DOTS strategy. So, a difference between the groups was obtained at the end of 2nd and 3rd month of treatment, with a higher microbiological convertion in CG than in SG. After 3 months of intensive phase, treatment failure was established at 6,7 % of patients of SG.

Impact on the general state and laboratory tolerance of TB-drugs used by different ways (injected or orally) at patients with hepato-biliary and pancreatic comorbidities was assessed through serological indices of albumine, bilirubine, transaminases, urea, creatinine and timol reaction. No differences were assessed before starting the treatment.

At the end of the intensive phase a higher level of albumine was established in CG. Timol test established a more elevated result in SG than in CG and indicates a higher drug-induced hepatotoxicity of oraly adminstered TB drugs. The established fact was proved by the elevation of bilirubine and transaminases in SG at the end of intensive phase. In CG elevation of serological biomarkers was established, but the statistical threshold was not achieved.

Radiation exploration of the hepatobiliary system established the increasing of the right liver lobe at 80,0% of all investigated patients with 0.7 ± 0,71 mm and resulted in a total length 15,1 ± 1,21 mm, the left liver lobe increased at 73,3% cases with 0,82 ± 0,12 mm with a total length 11,2 ± 2,7 mm, the signs of diffuse liver damage, expressed as hyperechogenic changes and increasing of the portal vein size were identified at 68,3% cases.

Conclusions

Assessing the differences between the clinical and laboratory tolerance of TB drugs according to the way of administration, it was proved the importance of individualization of the standard treatment in patients with hepatobiliary and pancreatic disorders and haplotypes (GSTM1+ / GSTT1 0/0, GSTT1+ / GSTM1 0/0, GSTT1 0/0 / GSTM1 0/0) by intravenous use of isoniazid and rifampicine in intensive phase, for improving the quality of the TB treatment.

The clinical improvement of the patient's general state under the influence of intravenous use of isoniazid and rifampicine was confirmed by a lower expressiveness of intoxication and bronchopulmonary syndromes, as well as by a better radiological dynamics and higher rate of microscopic convertion at the end of intensive phase of the TB-treatment.

Prospects for further research

Identification of other genes detoxication xenobiotics that may have an impact on treatment of tubercu losis.

References.1.Можливості фармакотерапії туберкульозу легень / Кужко М.М., М. Т. Клименко, Н. М. Гульчук [та ін.] // Туберкульоз, легеневі хвороби, ВІЛ-інфекція. - 2012. - №4 - С.57-64. 2.Наказ МОЗ України № 620 від 04.09.2014 р. "Уніфікований клінічний протокол первинної, вторинної (спеціалізованої) та третинної (високоспеціалізованої) медичної допомоги. Туберкульоз у дорослих". 3.Тодоріко Л. Д. Синдром системної запальної відповіді при поширених формах туберкульозу легень / Л.Д. Тодоріко // Укр. пульмон. ж. - 2013. - №3. - С.229-231. 4.Prevalence of inappropriate tuberculosis treatment regimens: a systematic review / MW Langendam, MJ van der Werf, E Huitric, [et al.] // Eur. Respir. J. 2011;26-28. 5.World Health Organization. Global tuberculosis control. Epidemiology, strategy, finances. // WHO Report, 2015. 6.A multiplex real-time PCR method for detection of GSTM1 and GSTT1 copy number / M. Timofeeva, B. Jager, A. Rosenberg [et al.] // Clin. Biochem. - 2009. - Vol. 42. - P. 500-509.

ЛЕЧЕНИЕ БОЛЬНЫХ ТУБЕРКУЛЕЗОМ ЛЕГКИХ С СОПУТСТВУЮЩИМ ПОРАЖЕНИЕМ ГЕПАТО-ПАНКРЕАТО-БИЛИАРНОЙ СИСТЕМЫ С УЧЕТОМ ДЕЛЕЦИОННОГО ПОЛИМОРФИЗМА ГЕНОВ СИСТЕМЫ ДЕТОКСИКАЦИИ КСЕНОБИОТИКОВ ГЛУТАТИОН-S-ТРАНСФЕРАЗЫ

И.А. Семьянив

Резюме. Результаты проведенного анализа засвидетельствовали о необходимости дифференцированного подхода в назначении программной химиотерапии при распространенном туберкулезе легких с патологией гепато-панкреато-билиарной системы и полиморфизмом генов системы детоксикации ксенобиотиков глутатион-S-трансферазы с применением инъекционных форм изониазида и рифампицина в интенсивную фазу лечения.

Ключевые слова: туберкулез, GST, инъекционные противотуберкулезные препараты.

ЛІКУВАННЯ ХВОРИХ НА ТУБЕРКУЛЬОЗ ЛЕГЕНЬ ІЗ СУПУТНІМ УРАЖЕННЯМ ГЕПАТО-ПАНКРЕАТО-БІЛІАРНОЇ СИСТЕМИ З УРАХУВАННЯМ ДЕЛЕЦІЙНОГО ПОЛІМОРФІЗМУ ГЕНІВ СИСТЕМИ ДЕТОКСИКАЦІЇ КСЕНОБІОТИКІВ ГЛУТАТІОН-S-ТРАНСФЕРАЗИ

І.О. Сем'янів

Резюме. Результати проведеного аналізу засвідчили про необхідність диференційованого підходу в призначенні програмної хіміотерапії при поширеному туберкульозі легень із патологією гепато-панкреато-біліарної системи та поліморфізмом генів системи детоксикації ксенобіотиків глутатіон-S-трансферази із застосуванням ін'єкційних форм ізоніазиду та рифампіцину в інтенсивній фазі лікування.

Ключові слова: туберкульоз, GST, ін'єкційні протитуберкульозні препарати.

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