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Analysis of Hepatotoxic Reactions During Treatment of Newly Diagnosed Patients with Pulmonary Drug Resistant Tuberculosis

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Abstract: 216 newly detected pulmonary tuberculosis patients suffring from multiple drug resistance (MDR) were examined. The patients were divided into 2 groups. The fist group consisted of 164 patients in whom when admitted to hospital, GeneXpert MTB/RIF was used to test the resistance of Mycobacterium tuberculosis (MTB) to rifampicin. Initially, patients in this group were treated with chemotherapy regimen 4 (pyrazinamide, kanamycin/amikacin/capreomycin, floroquinolones, cycloserine/terizidone, prothionamide, PAS). Group 2 included 97 patients. They all were treated with chemotherapy regimen 1 (isoniazid, rifampicin, pyrazinamide, ethambutol/streptomycin) before MDR was confimed in them by sputum culture on solid media (in 2-3 months of treatment) after that treatment regimen was amended with re-registration for chemotherapy regimen 4. It was found out that hepatotoxic reactions in patients without initial abnormal liver function when prescribing chemotherapy regimen 4 occurred in 31.3% of cases and when initially using regimen 1 followed by switching to regimen 4 – in 87.8% of cases ($p < 0.001$). In the course of treatment, the signs of liver damage in patients who initially received regimen 4 were more frequent in the fist 2 months of treatment, whereas in patients treated initially with regimen 1 with subsequent switching to regimen 4 – during the fist 4 months. In the overwhelming majority of cases, hepatotoxic reactions were mild in patients who initially received regimen 4 as well as in patients initially treated with regimen 1 followed by switching to regimen 4. However, severe hepatotoxic reactions were more often observed in patients from Group 2.

Key words: newly detected tuberculosis, multiple drug resistance, hepatotoxic reactions, chemotherapy

Introduction

One of relevant and priorities problems of modern phthisiology is increase in efficiency of treatment for the first time detected patients with lungs tuberculosis and multidrudresistance (MDR) of mycobacteria. The efficiency of treatment of this category of patients in many respects depends on timely definition of a range of the multidrudresistance (MDR)of mycobacteria of tuberculosis (MBT) and early diagnostics and correction of undesirable reactions to antituberculouse drugs (ATD) [1, 2, 5, 7]. Timely diagnostics of MDR MBT with use of molecular and genetic methods allows beginning

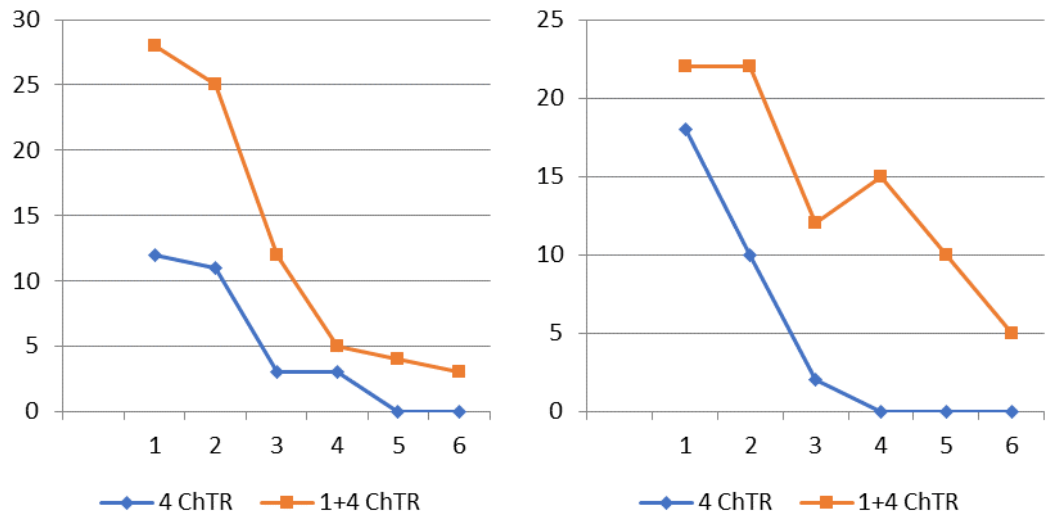
treatment of patients initially with the 4th rejime of chemotherapy (RChT). In the absence of opportunities of definition of a range of DR the fast methods use a crops method on dense nutrient mediums. Before data acquisition about MDR MBT (2-3 months of chemotherapy – ChT) treatment of these patients is carried out on 1 standard RChT. After data acquisition about MDRMBT the correction of treatment with a re-registration on the 4th RChT [4] is carried out. In literature there is a sufficient volume of information on influence of fast methods of diagnostics on efficiency of treatment of TB patients with MDR of the mycobacteria [3, 7]. There are no data on frequency and expressiveness of hepatotoxic reactions at application of such approaches to treatment.

Purpose: studying frequency and expressiveness of hepatotoxic reactions at application initially the 4th RChT and when assigning initially the 1st, and then 4th RChT at for the first time the revealed suffering from tuberculosis lungs with MDR MBT.

Materials and methods. Under observation were 216 newly detected patients with tuberculosis of lungs and MDR of the mycobacteria undergoing treatment in the center of phthisiology and pulmonology (Samarkand) during the period from march 2020 to june 2023. The research didn't join the patients having the accompanying pathology: HIV infection, oncological diseases, diabetes and also pregnant women. Patients were divided into 2 groups. The 4 RChT group was made by 134 patients at whom at receipt in a hospital the GeneXpert MTB/RIF method determined rifampicin resistance of MBT. Treatment of these patients was initially carried out on the 4th RChT (pyrazinamide, kanamitsin/amikatsin/kapreomitsin, ftorkhinolons, tsikloserin/terizidon, prothionamide, PASK). The 1 and 4 RChT group included 82 patients for whom MDR MBT diagnosed by method of crops of a phlegm on dense nutrient mediums. Before patients received treatment on the 1st RChT (an isoniazid, rifampicin, pyrazinamide, ethambutole/streptomycin). After data acquisition about MDR MBT (in 2-3 months of treatment) correction of treatment with a re-registration on the 4th RChT is carried out. In both groups men prevailed, and reliable differences between groups on a gender were absent (in the 4 RChT group of men there were 72.3%, in the 1 and 4 RChT group – 74.4%, $p> 0.05$; female-27.7 and 25.6% respectively, $p> 0.05$). The age of most of patients in both groups fluctuated from 18 to 49 years (76.9 and 75.6% respectively). The analysis of frequency of occurrence of various forms of tuberculosis of lungs showed that in both groups more than a half was made by patients with infiltrative tuberculosis (58.2 and 58.5% respectively, $p> 0.05$). Disseminate tuberculosis (35.1 and 37.8% respectively, $p> 0.05$) became the second in frequency among forms of tuberculosis of lungs in both groups. Other forms of tuberculosis of lungs were observed seldom. Significant differences between groups on the frequency of forms of tuberculosis of lungs were absent. Destructive changes in lungs were revealed in most of sick both groups ("4 RChT" –76.1% and "1 and 4 RChT" – 80.5%, $p> 0.05$). At the same time most of patients of both groups the sizes of cavities of disintegration had less than 2 cm (64.9 and 64.6% respectively, $p> 0.05$). Bacterial releasion it is revealed in the vast majority (94.0%) of patients in the 4 RChT group, at 10 (6.0%) patients existence of MBT was established only on DNA, and at all (100%) patients in the 1 and 4 RChT group. Poorly expressed tubercular intoxication was observed at 64.2 and 74.4% of patients in groups respectively ($p> 0.05$). Apparently from the provided data, there was no significant difference on groups. It gave the chance to compare the frequency and expressiveness of hepatotoxic reactions and their influence on efficiency of treatment in these groups of patients. At receipt in a hospital and also in the course of treatment of all patients surveyed with application of all-clinical methods, beam methods of diagnostics (including a computer tomography), microbiological methods of a research (the analysis of a phlegm on MBT by method of luminescent microscopy and crops on liquid and dense nutrient mediums, molecular and genetic methods – GeneXpertMTB/RIF), clinical blood test and urine, biochemical methods of a research, the ECG.

For identification of hepatotoxic reactions to application of ATD conducted a research of a functional condition of a liver on indicators of activity of enzymes of alaninaminotranspherase (ALT), aspartate aminotransferase (AST), the alkaline phosphatase (AP), γ-glutamiltranspherase (GGT), to the content of the general bilirubin. Researches carried out prior to treatment and further monthly. Monitoring and assessment of weight of hepatotoxic reactions were carried out on the five-point scale of CTCAE accepted in the international practice (Common Terminology Criteria for Adverse Events v.4.0 – the General terminological criteria for evaluation of the undesirable phenomena, version 4) [6]. According to these criteria, hepatotoxic reactions of easy degree of expressiveness (I degree) proceed asymptomatically or with insignificant clinical manifestations. At the same time the activity of ALT and AST enzymes exceeds the upper bound of norm to triple value, AP and GGT do 2.5-fold, the content of the general bilirubin – to 1.5-fold value. Moderately expressed hepatotoxic reactions (II degree) are shown by local clinical symptoms. At the same time values of activity of ALT and AST enzymes exceed the upper bound of norm from 3 to 5 times, AP and GGT-from 2.5 to 5 times, content of the general bilirubin – from 1.5 to 3 times. Heavy, clinically significant, but not life-threatening hepatotoxic reactions of the patient (III degree) are shown by the expressed clinical symptoms and values of activity of ALT, AST, AP and GGT enzymes exceeding the upper bound of norm from 5 to 20 times, content of the general bilirubin – from 3 to 10 times. At the hepatotoxic reactions having life-threatening consequences (IV degree), values of activity of ALT, AST, AP and GGT enzymes exceed the upper bound of norm more than 20 times, content of the general bilirubin – more than 10 times. The hepatotoxic reactions causing the death of the patient are estimated as reactions of the fifth severity. All researches were conducted according to requirements of biomedical ethics according to the Geneva Convention on human rights (1997) and the Helsinki declaration of the World Medical Association (2000) on the basis of permission of local ethical committee of the center of phthisiology and pulmonology. At all patients the written voluntary informed consent to participation in a research was received. Statistical processing of results is realized by means of the Excel and BIOSTAT software package. For each group calculated an arithmetic average (M) and an error of an average (m). An inspection of a hypothesis of equality of sizes at their normal distribution was carried out with use of t-criterion of Student. Distinctions were considered as statistically reliable at value $p < 0.05$. The assessment of interrelations of the studied indicators was carried out by calculation of coefficient of correlation of Spirmen which size was considered significant at $p < 0.05$. Determination of reliability of differences between quality indicators was carried out by means of criterion $\chi 2$.

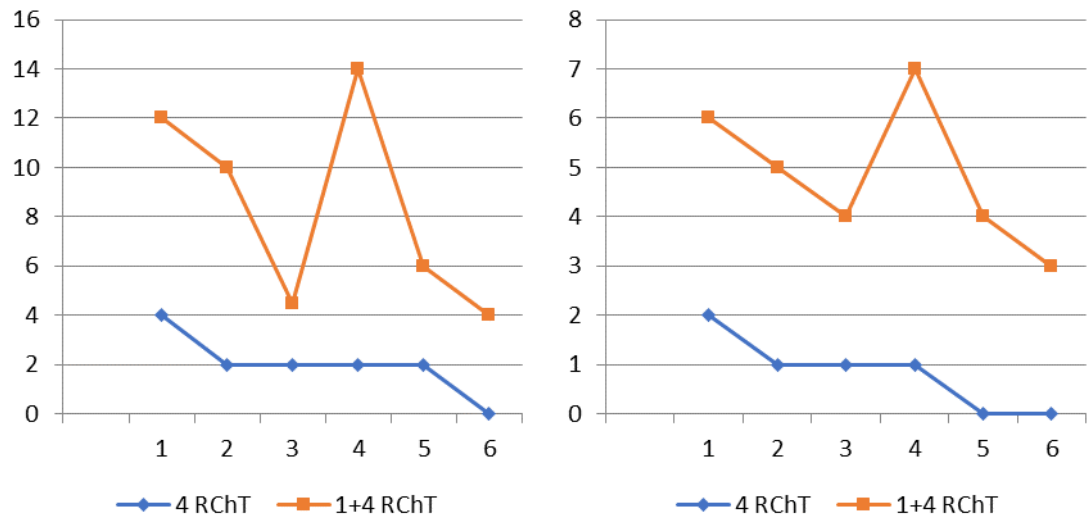
Results of a research. All patients prior to treatment had indicators of function of a liver within norm options. In the course of treatment among the studied indicators most often changes came to light in activity of ALT and AST. In 1 month of treatment in the 4 RChT group the number of patients with hyperactivity of ALT and AST made 18.6 and 13.4%, in the 1 and 4 RChT group – 21.5 and 26.8% respectively (fig. 1). Further in the 4 PXT group the number of patients at whom increase in activity of ALT and nuclear heating plant was for the first time observed began to decrease and to 2-month term made 10.4 and 11.9% respectively.



1 figure. Incidence of ALT, AST elevations in tested patients without prior hepatic impairment (%)

In the 1 and 4 RChT group in 2 months of ChT the increase in activity of ALT and AST was observed approximately with the same frequency, as well as in 1 month of ChT (21.5 and 23.8% respectively). In 3 months of ChT in the 4 RChT group the new cases of increase in activity of ALT and AST were observed only at 2.3 and 5.3% respectively. In the 1 and 4 RChT group to this term such patients were observed in 11.4 and 12.6% respectively that had significant differences between groups ($p < 0.01$). In 4, 5 and 6 months of ChT in the 4 RChT group didn't observe patients with for the first time the found increased values of activity of ALT, and in 5 and 6 months – AST. In the 1 and 4 RChT group the new cases of increase in activity of ALT and AST were observed for all 6 months of ChT. In 2, 3, 5 and 6 months of ChT the frequency of identification of signs of a tsitoliz (increase in activity of ALT and AST) in the 1 and 4 RChT group was significantly higher in comparison with the 4 RChT group.

The similar picture was observed in the analysis of activity of AP and GGT (fig. 2). Increase in activity of SF and GGT in both groups of patients came to light in 1 month of treatment. In the 4 RChT group since 2nd month of ChT the number of patients with for the first time the revealed increased values of activity of AP and GGT steadily decreased and by 6th month of such patients wasn't observed. In the 1 and 4 RChT group the increase in activity of AP and GGT in 1 month of treatment was observed more often in comparison with the 4 RChT group. In 2 months of ChT the number of such patients remained at the previous level. Growth of number of patients with increase in activity of AP and GGT was observed in 4 months of treatment again. Since 5th month the number of such patients decreased and remained at the same level and in 6 months of ChT. On all terms of observation the patients with for the first time the revealed increased AP and GGT values were observed in the 1 and 4 RChT groups (fig. 2) authentically more often. At 10 (6.1%) patients in the 4 RChT group and at 15 (15.4%) in the 1 and 4 RChT group the dysfunction of a liver came to light only in the form of increase in activity of GGT. Increase in content of the general bilirubin in blood serum in the 4 PXT group was observed only in 2 and 3 months of treatment – on 3.7 and 2.3% of patients respectively. In the 1 and 4 RChT group such patients came to light more often, and increase in average values was in 1 month of treatment (tab). The analysis of change of quantitative indices of function of a liver showed that at sick both groups the average values of indicators of function of a liver (ALT, AST, AP and GGT) on all terms of observation exceeded normal values.



2 figure. Incidence of new increases in IF and GGT activity in tested patients without prior hepatic impairment (%)

At the same time on all terms of observation the average values of these indicators in the 1 and 4 RChT group were significantly higher in comparison with the 4 RChT group (tab). Besides, minimum – the maximum indicators patients of the 1 and 4 RChT group had amplitude more. In the 4 RChT group the highest values of average and maximum values of function of a liver observed in 1 month of ChT, further they decreased. In the 1 and 4 RChT group the maximum values of average and maximum values of function of a liver observed in 2 and 3 months of ChT, further (in 4, 5 and 6 months of ChT) these indicators decreased. Studying safety of hepatotoxic reactions showed that the activity of ALT in 1 and 2 months of ChT in both groups at the vast majority of the patients having violations exceeded the upper bound of norm to 3 times (the I degree on CTCAE scale) (fig.2). Heavy (the III degree on CTCAE scale) the hepatotoxic reactions which are shown increase in activity of ALT from 5 to 10 times in 1 month of ChT in the 4 RChT group were observed in 4.0%, and in the 1 and 4 RChT group – in 9.5% of cases. Since 2nd month of ChT and until the end of observation in the 4 RChT group such patients didn't come to light. In the 1 and 4 RChT group in 2 months of ChT 11.2% of patients had an increase in activity of ALT from 5 to 10 times, and in 3 months reached 22.2% (fig.2). Since 4th month of ChT the increased ALT values in the 1 and 4 RChT group weren't observed. In the 4 RChT group the increase in activity of ALT in 4, 5 and 6 months of ChT wasn't observed. Changes of activity of AST in the course of treatment in the compared groups were similar to changes of ALT. The activity of AP in the 4 RChT group throughout the entire period of observation exceeded the upper bound of norm up to 2.5 times (the I degree on CTCAE scale). In the 1 and 4 RChT group in 2 months of ChT at 37.5% and in 3 months of ChT at 16.7% of patients the increase in activity of AP was estimated as the II degree on CTCAE scale. Further (in 4, 5 and 6 months of ChT) increase in activity of AP had the I degree on CTCAE scale. The activity of GGT in 1, 2 and 3 months of ChT approximately at ⅓ sick both groups exceeded the upper bound of norm to 2.5-5 times (the II degree on CTCAE scale). The third degree on a scale of CTCAE was observed only at patients of the 1 and 4 RChT group in 1 and 2 months of treatment. Since 4th month of ChT the patients of both groups had an increase in activity of GGT of easy degree.

Total bilirubin in patients in both groups exceeded the upper limit of normal by up to 1.5 times during the entire follow-up period and was assessed as grade I on the CTSAE scale. In general in the 4 RChT group for the first time hepatotoxic reactions arose at 42 (31.3%) from 134 patients, and in the 1 and 4 RChT group – at 72 (87.8%) from 82 patients ($\chi 2 = 12.8$; $p = 0,001$). Correlation analysis revealed that enzymatic indicators of liver pathology in examined patients were closely

interconnected. Correlation coefficients between ALT levels with AST were 0.721 (p = 0.01), AST with total bilirubin – 0.76 (p = 0.01), ALT with GGT - 0.677 (p = 0.01), and with total bilirubin-0.204 (p = 0.05), GGT with total bilirubin -0.285 (p = 0.02). Clinical symptoms of liver damage were observed in 41 (15.7%) patients out of 261: in 14 (8.5%) patients of the "4 RChT" group and in 27 (27.8%) patients of the "1 and 4 RChT" group ($\chi 2$ = 4.11; p = 0,042). They were manifested by pain and severity in the right hypochondrium, nausea, vomiting and stool disorders, in some cases – the ictericity of the skin and visible mucous membranes. Patients with newly occurring hepatotoxic reactions were prescribed hepatoprotective, antispasmodic, choleretic and detoxification therapy, which made it possible to eliminate clinical and laboratory manifestations of liver damage or significantly reduce them. In the "4 RChT" group, due to the development of hepatotoxic reactions, it was necessary to temporarily discontinue ChT in 17.6% of patients, and in the "1 and 4 RChT" group - in 42.3 (p < 0.01).

Conclusion. The results of the study in newly diagnosed patients with pulmonary tuberculosis with MDR of the pathogen without initial liver function disorders showed that in the group of patients initially receiving the 4th RChT, hepatotoxic reactions occurred less often compared to patients treated first with the 1st RChT, and after 2-3 months – with the 4th RChT. Most often, changes were detected in the form of increased ALT, AST and GGT activity. In the group of patients initially receiving the 4th RChT, hepatotoxic reactions were observed in the first 2 months of ChT, then their frequency decreased, and in the 5th and 6th months of ChT – was absent. In the group of patients treated with the 1st RChT, and after 2-3 months. According to the 4th RChT, hepatotoxic changes were observed with a high frequency during the first 4 months of ChT. Only by the end of the 5th month ChT their frequency decreased. Hepatotoxic reactions (CTCAE grade III) in the 4 RChT group were observed only after 1 month of ChT, and in the 1 and 4 RChT group during the first 3 months of ChT. The obtained data indicate that the introduction of rapid methods for diagnosing MBT MDR in TB institutions allows the initial prescription of the 4th RChT, in which hepatotoxic reactions are observed less often and are less pronounced.

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