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THERAPY OF PULMONARY TUBERCULOSIS WITH MULTIDRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS USING TIOUREIDOIMINOMETHYLPYRIDINIUM PERCHLORATE (PERCHLOZON)

I. Chernokhaeva[1], M. Pavlova[1], A. Starshinova[1], N. Sapozhnikova[1], E. Belaeva[1], V. Zhuravlev[1], L. Archakova[1,2], Piotr Yablonskii[1,2]

[1]St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg

[2]Sankt Petersburg State University, St. Petersburg

Corresponding author: Anna Starshinova (Research Institute of Phthisiopulmonology, 191036, Ligovskii pr.2/4, St. Petersburg, Russian Federation), +79052043861, starshinova_777@mail.ru, drannastarshinova@gmail.com

Abstract- Currently efficacy of therapy of patients with MDR TB does not exceed 48.7% worldwide and in Russian Federation. One of the reason is a frequent development of adverse drug reactions during the use of combination of antituberculosis drugs. Since 2013 after registration of tioureidoiminomethylpyridinium perchlorate (Pecrhlozon®) in Russian Federation, opportunities appeared for further study of its efficacy and safety in treatment of tuberculosis with multiple drug resistance (MDR). In the present study we applied monitoring of adverse drug reactions during complex therapy by Perchlozon in combination with five other drugs with the use of international 5-grade scale. We used Common Terminology Criteria for Adverse Events (version 3.0). In the study only mild (grade 1) and moderate (grade 2) adverse drug reactions were observed except single case when severe (grade 3) adverse drug reaction happened. Mild adverse reactions that during receiving Perchlozon therapy in complex with other drugs for MDR-TB did not require its cessation.

Key words: therapy, multiple drug resistance, Perchlozon.

I. INTRODUCTION

Currently efficacy of therapy of patients with MDR TB does not exceed 48.7% worldwide and in Russian Federation [1, 2], it brings about frequent development of adverse drug reactions during administration of antituberulosis drugs combination [4, 5].

Incidence of adverse drug reactions during antituberulosis therapy reaches 62–65 % [6]. Development of adverse drug reactions on anti-TB chemotherapy requires their monitoring and corrective measures. Since 2013 there is an opportunity to use new medication - Pecrhlozon.

The drug has clear selecting inhibitory effect on viability of M. tuberculosis (MBT). It has significant antituberculosis effect against both concerning drug sensitive and drug resistant MBT, and it is recommended for treatment of MDR TB [7,8]. Further study of safe of medication in clinical practice can extend knowledge about Pecrhlozon use and can help physicians prevent adverse drug reactions at a complex therapy with MDR TB in order to raise efficacy of treatment.

Objective: to perform monitoring of adverse drug reactions during complex therapy with Pecrhlozon of MDR-TB.

II. MATERIALS AND METHODS

At phthisiopulmonology department 25 patients since 2013 to 2014 were treated: 9 males and 16 females at the age 18-70 years. They were treated by complex therapy because of: infiltrative pulmonary tuberculosis (16,0%; 4), infiltrative pulmonary tuberculosis in phase of degradation and seeding (56,0%; 14), disseminated (8,0%; 2), cavernous (8,0%; 2), fibrous- cavernous tuberculosis (12,0%; 3). All patients have MDR TB. Practically all patients had resistance to Streptomycin (84,0%; 21), majority – to Ethambutol (68,0%; 17), every fourth - Ethionamide (20,0%; 5), to Protionamide (8,0%; 2), to Ofloxacin - 16,0% (4), to Kanamycin - 8,0% (2), to Capreomycin - 4,0% (1), and to Pyrazinamide - 4,0% (1). All patients were diagnosed for the first time.

The duration of treatment by combination of 6 drugs (Perhloson, Pyrazinamide, Capreomycin , Ethambutol / Protionamide / Ethionamide, Cycloserine/ Terizidon and paraaminosalicylic acid – was of 6 months. Normal daily doze of Perchloson was used – 10 - 12 mg/kg. Administration after its registration for use in clinical practice of Perchloson with duration 6 months is in line with information on drug [9]

Inclusion criteria: age of patients 18-70 years, presence mutations, presence newly diagnosed lungs TB with bacterial excretion, mutation of MBT associated with resistance at least rifampicion and izoniazid, detected by molecular – genetic methods (MGM).

Exclusion criteria: presence in anamnesis of tumorous diseases, severe or chronic somatic diseases at the stage of decompensation, absence of MDR, including presence of resistance M.tuberculosis at the same time to aminoglycosides og fluoroquinolones (i.e. XDR), patients with HIV, presence of intolerability in anamnesis to drugs used in the scheme of the study, TB of the other localisations, including generalization forms.

At hospital complex examination was done realized with evaluation of intensity of clinical symptoms and signs, X – ray changing, with examination of sputum for presence of M.tuberculosis and identification variety of drug resistance. Complex of X-ray examination included plain X-ray and spiral computed tomography of breast (tomograph “AQUILION-32”). Laboratory complex of diagnosis included luminescent bacterioscopy, seeding

diagnostic substance on solid medium and fluid medium, identification DNA M.tuberculosis by real time PCR, GeneXpert. Every 2 weeks we performed evaluation of renal, liver functions and system condition by clinical and biochemical analysis of blood and urine.

The main criteria of short-term efficacy of therapy were: resolution of clinical appearance and respiratory signs of the disease, cessation of bacterial excretion, decrease of infiltrative foci and disappearance of cavernous foci in lungs by X-ray. Outcome analysis was realized in 3 months and 6 months from the beginning of therapy.

Monitoring and evaluation of advers reactions were done in accordance with accepted in international practice five grade-scale [11]. Treatment of adverse reactions was done in line with applicable guideline [10].

Statistical analysis of study data was performed by SPSS 16.0. Interval data were evaluated in the form of M±SD, where M – arithmetic average, SD- standard deviation. Variance analysis was underway, measures was supposed to be significant at $p<0,05$. Estimation of measures were performed relative risk (relative risk (RR)), correlation prospects (odds ratio (OR)).

III. RESULTS AND DISCUSSION

On completion of intensive phrase we analyzed efficacy of chemotherapy by 3 and 6 months. Resolution of intoxication symptoms was already registrated by 1 month of therapy in 60% (15). By 3 months of therapy respiratory symptoms and stopping intoxication were not registrated in 80 % (20) cases.

Cessation of bacterial excretion was reached in 72% (18) by 3 months; and practically in all patients according to results of bacteriologic examination by 6 months, in 96% (24), by 8 month – 96% (24), by 12 month – 100% (25) with positive x-ray dynamics of lungs (absorption of infiltrative changes, decreasing of cavernous and their closure (80%;20) by 12 months.

Monitoring adverse reactions in group showed, that frequency of their in emergence is 76,0% (Cl 95% 56,0-4,0; RR=0,7; OR=3,16). Results of adverse reactions monitoring according to systems are presented in table 1

Table 1. Monitoring of advers reactions in accordance with the programme "Evaluation criteria of advers affects, version 3.0"

Advers reactions	Parameters			
	%	n	RR	OR
GI tract	56,0	14	0,5	**1,3**
Metabolic reactions	44,0	11	0,4	0,8
Neurologic	28,0	7	0,3	0,4
Endocrine	18,4	9	0,4	0,5
Skin reactions	32,0	8	0,3	0,5
Cardiotoxic disorders	28,0	7	0,2	0,4
Allergic advers reactions	8,2	4	0,2	0,2

In accordance with evaluation of advers reactions, all reactions were of 1-2 grade severity, which are mild (appearing symptoms, that were resolved administration symptomatic treatment and moderate (2) (symptoms were resolved after prescription of adequate therapy). In single patient advers reactions of 3 severity grade were observe. Adverbs reactions of 4-5 severity were not observed.

Reaction of GI-tract were reported in 56.0 % (14) cases and occurred as diarrhoe (1 grade – 85.7%, 2 grade – 7.1%; 3 grade – 7.1%), vomiting (1 grade – 85.7%; 2 grade -14.2%). OR of these reactions in significant.

Hepatobiliary abnormality, which are characterized by emergence of cholecystitis, compromised liver function (emergence of icterus, tremor, hepatic coma), functional changing of pancreas and emergence pancreatitis were not recorded in groups. Accorging to CTCAE, metabolic disorders were observed, which indicated in 44.0 % and were characterised by increasing GPT, AST and level of bilirubin. Intensity of these reactions was 1 degree (elevation of GPT, AST up to 2,5 times, bilirubin up to 1,5 times higher normal range) - in 81.8% (9) and 2 degree (rising measures GPT, AST up to 2,5 – 5.0 times, bilirubin up to 1,5 – 3,0 times higher normal range) – in 18,2 % (2) cases.

At occurrence of metabolic disorders symptomatic treatment was administrated to patients [10]. At 1 degree toxicity, the drugs were not interrupted, during 2 degree – drugs were put on hold and were restated after decreasing of abnormalities. Most often (80 %) decreasing of abnormalities happened by 5-6 day of treatment, and their normalization by 10 day.

Neurologic reactions (somnolence, dizziness) were registrated in 28 % (1). Two patients developed disorientation of 1 degree.

Dermatologic adverse reactions were observed in 32.0 % in groups (8). Presence of rash with peeling itch, acneiform rash, urticarial were reported. In 80 % cases changes were 1 grade of severity, apart from 3 patients, who had adverse reactions of 2 grade of severity (skin rash with itch which demanded application of symptomatic treatment). So no discontinuation of Perchlozon was required.

General cardiotoxic disordes were observed in 28,0% (7) cases. All changes were 1 level of severity and was registrated at ECG. Disordes did not require additional therapy. Case follow-up was carried out.

Endocrine adverse reactions (changing level of glucose in blood in the presence of diabetes mellitus(2); water retention, somnolence, low blood pressure when hypothyroidism (6)) were in 18,4 % (9). These changes did not depend on gender and were observed equally both males – 44 % (n=4), females – 56 % (n=5), did not cause difficulties during daily activities, but required prescription of a corrective treatment under observation care of endocrinologist and were estimated as 2 grade of severity.

At occurrence of drug hypothyroidism after assessment of thyroid gland functions by endocrinologist,

but stopping Perchloson was not demanded – after studying of thyroid function and consultation of endocrinologist.

Allergic advers reactions (combination of transient rash, urticarial and fever, fever) were recorded in 8.2% (4), they were followed by fever higher than 38C, and were classified as 2 grade of severity.

Thus, complex therapy with Perchloson showed its high efficacy in treatment of respiratory tuberculosis. The highest risk of adverse reactions occurrence is from GI tract. According to results of adverse reactions monitoring all reactions were not higher than 1-2 grade of severity, it characterises low toxicity of the therapy scheme reported.

A. Clinical case

Patients G. (1985 year of birth, №884). Admission diagnosis: infiltrative TB of superior lobe of right lung in phase of degradation and dissemination MBT(+), MDR (S, H, R, Et).

Co-morbidity is absent. Medical history: patient did not have prior TB in anamnesis, contact with TB -ill patients was not reported, regular X-ray assessment (last one 31.10.12 to abnormality was diagnosed). Since 27.08.2013 to 24.09.2013 patient was received medical treatment in hospital RAN with diagnosis of exogenous allergic alveolitis, non-hospital pneumonia. Patients received nonspecific antimicrobial therapy (tavanic), Dexamethasone.

According to presented discharge summary MH №3090, patient was discharged with positive X-ray dynamics. At of control spiral computed tomography (SCT) of breast in 2 months infiltrative changes remain. Patient was referred for hospitalization to therapy department. At entry patients complained about fever, lack of energy, cough with mucous expectoration. Auscultation: rough respiration in lungs, no crepitation, cardiac sound is rhythmic, pulse is 86 beats per minute with satisfying repletion. ECG: sinus rhytm, partial right bundle branch block. No abnormality of Ear Nose Throat organs. Aminoglycosides are not contraindicated. No abnormality of visual organs. Echocardiogram (28.01.2014): aorta is not enlarged, inspissated. Heart chambers are not enlarged.

Sputum examination on presence of MBT by bacterioscopy method is positive. Sputum examination using bacterioscopy MBT (+). Sputum examination by PCR – DNA MBT was registrated and mutations were found out, which are responsible for resistance to izoniazid and rifampicin. Sputum examination by using method of BACTEC – resistance was identified to S, H, R, Et.

According to X-ray examination using MSCT (16.01.2014), in subiculum of right lobe of the lung and in C6 right infiltration with presence of smalls atriums (Fig.1)

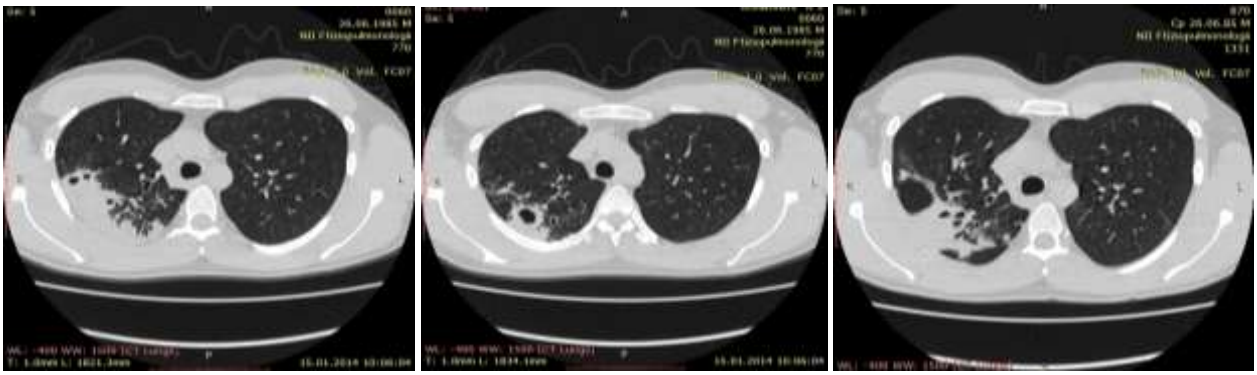

Fig. 1 Patient G. CT of breast at entry.

Sheme of therapy was prescribed: Perhloson (800 mg) – taking into account of body weight, Pyrazinamide (1,5 mg), Capreomycin (1,5 mg), Ethambutol (1,2 mg), PASK (9,0 mg), Cycloserine (0,75 mg).

On the background of therapy intoxication symptoms disappeared during the first month, patient gained 1.5 kg in weight. Temperature was normal, cough happened more rarely, there was decrease in sputum excretion. By the second month of therapy symptoms of intoxication and respiratory symptoms were resolved completely. Patient gained 2,5 kg in weight. Good drug tolerance was observed, psychoemotional condition of patient became better.

B. Negative results of bacterioscopy were received.

In 3 months of therapy negative results on the presence of MBT by bacterioscopy, negative seeding on liquid medium. Sputum by seeding method on the presence MBT-negative (-). According MSCT of breast– reducing infiltration and decreasing atriums of degradation. (Fig. 2)

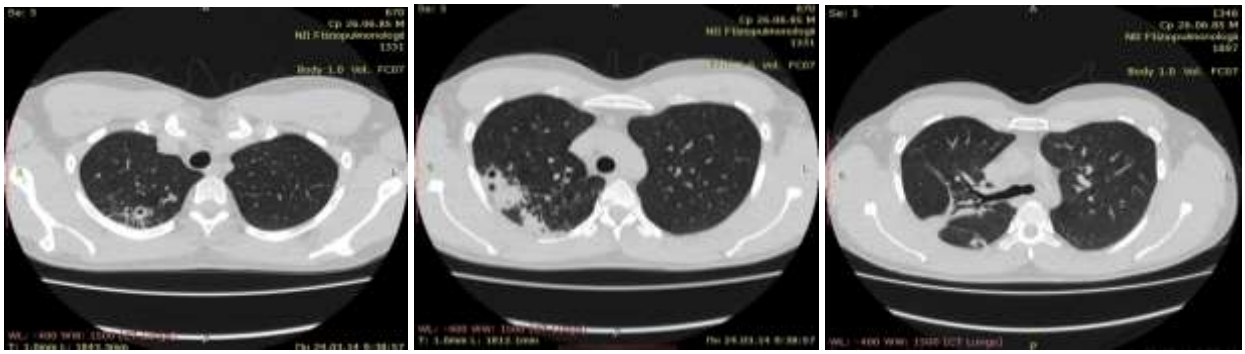

Fig. 2. Patient G. CT of breast in 3 months of therapy

By 3 months of therapy there was complaints on facial swelling, mild fatigue, low pressure, somnolence appeared. Endocrinologist consulted the patient. According to laboratory diagnosis, rising level of thyroid hormones was recorded. TTH in a month with consequent correction of hormonal replacement therapy, monitoring by endocrinologist.

By 6 moths negative results were registrated on the presence MBT in sputum. According to laboratory diagnosis level of thyroid hormones over time (15.07.14) was improved. According to U/S of thyroid hormones in dynamic. According to CT of breast (09.06.14): decreasing of infiltration in superior lobe of right lung, closing atriums in subiculum C3 on the right, cavity paries become thinner on the line C1 and C2 on the right . In the others parts of lungs there is no foci and infiltration (Fig. 3)

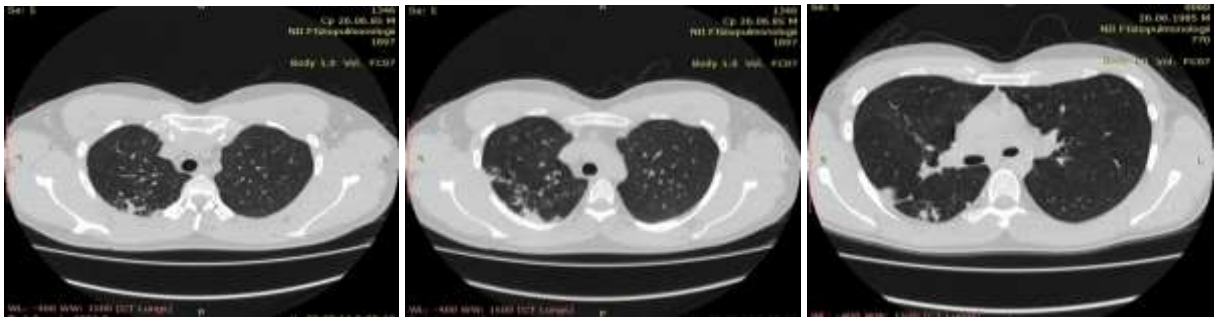

Fig. 3 Patient G. CT of breast in 6 months of therapy.

By 12 moths negative results were registrated on the presence MBT in sputum. According to CT positive dynamic, of lungs there is no foci and infiltration (Fig. 4)

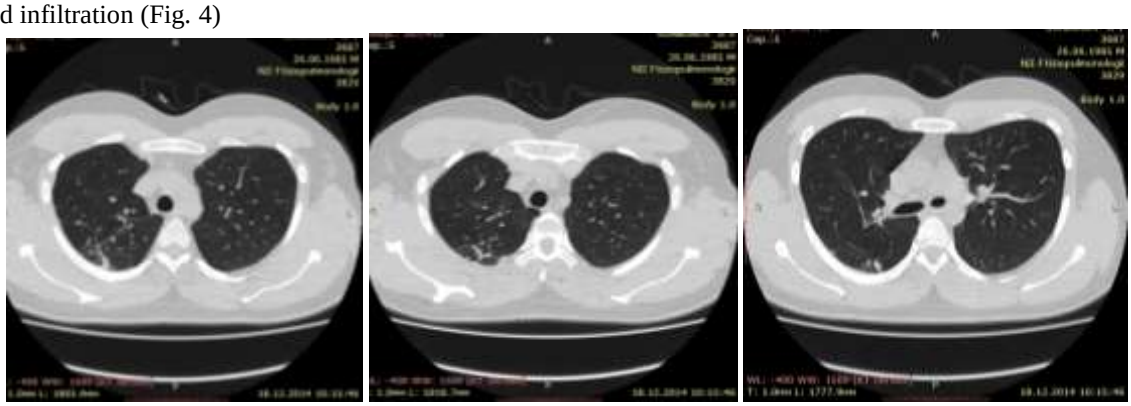

Fig. 4 Patient G. CT of breast in 6 months of therapy.

Patients moved to the phase of extended course of main treatment. The findings clearly demonstrate high effectiveness of Perhloson in combination with 5 antituberculosis drugs.

IV. CONCLUSION

Using thioureidoiminomethylpyridinii (perchloson) in complex therapy of lung TB with multiple drug resistance. Adverse reactions matched mild and moderate severity. Occurrence risk of GI tract reactions is the most significant among others adverse reactions, but its eliminating can be achieved by standard measures and does not require the drug is not necessary to stop drugs. Mild adverse reactions, developing on the background Perchloson administration, do not demand discontinuation of treatment. Early correction of adverse reactions allows to keep high efficacy of main therapy with Perchloson.

REFERENCES

[1] Tuberculosis in the Russian Federation 2011, 2013. Analytical Review. - Moscow-280p.

[2] Yablonskii, P.K., 2013. Russian phthisiopulmonology today - the choice of development path, J. Medical Alliance; 3. -P. 5-24.

[3] Sterlikov, S.A., 2014. Pulmonary TB patients characteristics and main results of treatment of newly diagnosed registered in 2011, J. Tuberculosis and Lung Disease. – 7. - P.16-20.

[4] Ivanova, L.A., M.V. Pavlova, L.I. Archakova, 2003. Tactics of treatment of patients with drug-resistant pulmonary tuberculosis, J. Problems. Tuberculosis and Lung Disease. - № 5. - C. 14-16.

[5] Perelman, M.I. et al., 2003. Treatment of drug-resistant TB, , J. Antibiotics and chemotherapy, 8- P. 28-36.

[6] Nizova, A.V. et al., 2007. Analysis of drug resistance Mycobacterium tuberculosis with drugs first and second line. - J. Epidemiology and infection. Disease; 4.-P.7-11.

[7] TB drugs Perhlozon ® in complex treatment of pulmonary tuberculosis: guidelines. - St .; Irkutsk, 2013.- 32c.

[8] Vinogradova, T. et al, 1994. " Perchlozon" - a new compound with high antituberculosis activity. J. Chemistry of drugs. - St. Petersburg, - P.94-95.

[9] Vinogradova T., Zabolotnykh N., Vitovskaya M,. VasilievaS, Malygina E., 2007. Evaluating the effectiveness of chemotherapy regimens of drug resistance of experimental tuberculosis. Psihofarma, Biol., Substance abuse.- V.7, spec. Issue (Part 1). - P.168.

[10] Yablonsky P.K., 2013. Clinical recommendations for diagnosis and treatment of pulmonary tuberculosis in adults [El. resource]/ edited.; National Association of TB specialists.- 48c. - www.naph.ru.

[11] Common Terminology Criteria for Adverse Events V3.0. Cancer Therapy Evaluation Program. - December 12, 2003.