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THE COMPARATIVE ANALYSIS OF EFFECTIVENESS OF TREATMENT WITH ANTI-TB DRUGS OF THE 1ST AND 2ND LINES FOR CHILDREN AND ADOLESCENTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

The paper shows results of study on comparative treatment effectiveness in children and adolescents with from multi drug resistant tuberculosis MDR TB (2000-2008) treated with anti-TB drugs of the 2nd line (80 patients) and 1st line (80 patients) in the Kazakhstan. It was stated in patients with MDR TB that outcomes of treatment were successful in 91.2%, but relapse development of TB disease occurred in 12.7% of cases, and 5 (6.2%) patients died (P ≤0.05). Thus, patients with MDR TB need to be treated with anti-TB drugs of the 2nd line accordingly to their DST.

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Introduction

Today in Kazakhstan fight against tuberculosis remains the important strategic objective and priority line of the public health. During last years in Kazakhstan TB incidence among adults and children have been stabilized somewhat, but indicators of TB incidence among adolescents remain higher (Statistical Review on Tuberculosis in the Republic of Kazakhstan,

1979-2008). As some investigations show, characteristics of the epidemiological situation on TB among children population was significant since it is not only the quantitative evaluation of indicators, but the qualitative one that allows to give the prognostics in TB situation in general (Aksenova, 2002; WHO 1998-2003, Nyazbekova, 1987). In Kazakhstan (RK) tendency to increasing the number of drug resistant TB appeared among children and adolescents and the questions of treatment and management of those cases are discussed up to day, as in the majority of them poly-resistance of M. tuberculosis (MBT) (to three drugs or more) is revealed (Amin, 1990; Auregan, 1997; Blower et al., 1995; Zhusupova et al., 2006; Zhadnov et al., 2001; Ismailov, 2006; Okulovskaya, 1998; Ovsyankina, 2000; Okulovskaya et al., 1999; Prijmak et al., 1984).

Growth of incidence of resistant TB forms among children and adolescents is due to the great pool of TB infection including MDR TB (Zuber et al., 1997; Needle and Ball, 1997; Sudre et al., 1997; Ramasnamy and Musser, 1998; Rieder et al., 1990; Rieder, 2001). Increase in number of TB treatment failures among children by two times, and among adolescents by three times is the evidence of this. Treatment with anti-TB drugs of the first line (DFL) for those children and adolescents is non effective since the resistance to them leads to forming the drug resistant tuberculosis and needing to implement the anti-TB drugs of the second line (DSL) to which (MBT) are sensitive.

In literature sources there are the limited number of works dedicated to the study of the follow-up outcomes of drug resistant TB among children and adolescents (Ovsyankina, 2000; Serikbaeva et al., 2002; Serikbaeva, 2004).

Target of our investigation is the comparative analysis of effectiveness of MDR TB treatment in children and adolescents with anti-TB drugs of the first and second lines and study of outcomes and follow-up outcomes of TB treatment.

Materials and method

Method of retrospective cohort investigation was implemented to study the drug resistant TB forms among children and adolescents treated with anti-TB drugs of the first and second lines.

The cases of TB in 160 children and adolescents treated since December 26, 2000 till December 25, 2008 were included in our analytical investigation. Tuberculosis process was characterized by presence of tuberculosis mycobacteria emission and drug resistance confirmed to the drugs of the first line. Database on children and adolescents treated from 2000 to 2008 by reason of drug resistant TB in RK with anti-TB drugs of the second line (Group 1 - 80 patients) and with drugs of the first line (Group 2 - 80 patients) was selected for comparative study of treatment outcomes.

The informative agreement from all patients and their relatives for investigation and treatment was obtained.

In order to clarify the causes of drug resistant TB development among children and adolescents we elaborated a special card reflected the factors as followed: gender, age of a patient, social and financial status, living conditions, family status, presence of concomitant diseases, presence of BCG scar, contact with TB source, clinical TB form, type of a patient, drug sensitivity test, duration of the intensive and continuation phases of the treatment. There were taken into account the follow-up control over outcomes of treatment with the drugs of the first line and the drugs of the first line after stopping the dispensary notification (DN), i.e. the successful treatment or TB disease relapse and, besides this, durability and regularity of the dispensary notification (DN) by group I and group II of DN etc.

There were implemented the laboratory methods (routine clinical investigations, sputum microscopy and culture investigation, DST), and clinical methods (anamnesis, physical examination, auscultation, palpation, percussion)

The medical card of a clinical patient (form 003\u) and out-patient disease history (form 025\u) were the instruments for data collection.

The statistical analysis was conducted through implementation of the advanced program complexes Microsoft Windows XP (Service Pack 3), Microsoft Excel (version 2007). To perform the analysis of data DBF fail was conducted through Programme SPSS Version 16 (Chicago, USA).

To conduct the comparative analysis of outcomes of the treatment of patients with MDR TB treated with anti-TB drugs of the first and second line test was implemented for comparison of two or more independent samples, dispersion analysis (ANOVA).

Results

It was determined that adolescents (62.3% and 53.8%), females (60.9% and 60.0%), urban inhabitants (56.5% and 65.0%) were prevalent in both groups relatively. Thus, the groups for comparison were virtually identical.

The most significant risk factor for TB infection and TB disease development was the contact with adult TB patient (F=7.340). In the Group 1 TB contact was revealed in 71.0%, including the family contact with a patient with MDR TB in 63.7%, contact with a relative suffered from TB in 5,9%, more rarely it was a school contact in 1.4%. TB source was not found-out in 29.0%. Thus, in the majority of patients TB contact was revealed, and in two thirds out of them it was proved the contact with MDR TB patient.

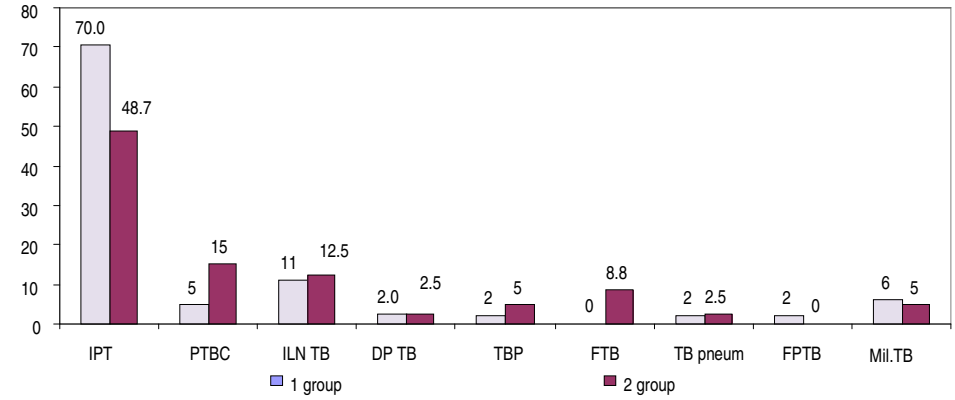
In the Group 2 contact with TB source was revealed in 47.5% of cases including source with MDR TB in 26.1%, a contact with a relative in 10.6%, more rarely it was revealed the school contact and occasional contact in 6.6% and 4.2% relatively. TB source was not found out in 52.5%. I.e. children and adolescents of the Group 2 had the continuous and

durable contact with sputum smear positive TB case lesser than in a half of cases (P ≤0.05).

The following risk factor, by its significance for children and adolescents with MDR TB, was the presence of concomitant diseases (F=5.243). In both groups they occurred in 97.1%, mainly in term of anemia in 37.3%, gastrointestinal diseases in 31.3%, diseases of CNS in 17.9%, more rarely diseases of urinary system, endocrine system (diabetes mellitus) and cardiovascular system (in 8.9%, 2.9%, 1.5% relatively).

The structure of TB incidence among children and adolescents corresponded mainly to the peculiarities of TB courses in the appropriate age period. As it is shown in the picture 1, infiltrative pulmonary tuberculosis (IPT) was prevalent in both groups - 70.0% and 48.7% relatively. The primary TB forms were prevalent among children, TB of intrathoracic lymphatic nodes (ILN TB) occurred the more frequently (11.0% and 12.5% relatively). The disseminated pulmonary TB (DP TB) and caseous TB pneumonia were revealed with the nearly similar frequency (2.0 и 2.5% relatively). The primary TB complex (PTBC) occurred more rarely - in 5.0% and 15.0% relatively, and the miliary TB (Mil.TB) did in 6.0% and 5.0%. The limited processes in term of focal TB (FTB) and tuberculosis pleurisy (TBP) in children and adolescents with MDR TB were revealed mainly in patients of the Group 2 (8.8% and 5.0%). The fibro-cavernous pulmonary TB (FPTB) was diagnosed in one patient (2.0%) treated with anti-TB drugs of the second line.

FIGURE 1. THE CLINICAL STRUCTURE OF TB IN CHILDREN AND ADOLESCENTS TREATED WITH DRUGS OF THE 2ND LINE (GROUP I) AND 1ST LINE (GROUP II)



The prevalent location of TB process was unilateral in both groups - 57.9% and 74.7% relatively. Thus, disease of the primary genesis and its limited forms occurred more frequently among patients of the Group 2, that why, despite of the presence of drug resistance of MBT to the drugs of the first line, they were treated with the drugs of the first line yet. Secondary and advanced TB forms were revealed mainly in patients of the Group 1 which were administrated the drugs of the second line after testing drug resistance.

The complicated processes took place in the children and adolescents of both groups (100.0% and 22.4%). But frequency of complications was lower among patients of the Group 2 observed: thus, bronchial TB was diagnosed in 37.0% and 11.2% relatively, TB pleurisy in 33.0% and 11.2%, hemorrhage, lung tissue destruction and atelectasis were found-out in 26.0%, 2.0% and 9.0% (P≤0.05) relatively.

Also, the destructive processes were revealed in 81.2% of patients in the Group 1 while in the Group 2 destruction cavities were present in 28.2% ($P \leq 0.01$) of children and adolescents only which continued their treatment with the drugs of the first line.

There were marked the differences in detection of MBT by microscopy method yet. Thus, M. tuberculosis were identified in 62.3% of patients of the Group 1 while it did in 30.0% ($p \leq 0.05$) ($F=3.406$) of the Group 2 only.

The majority of patients (68.1%) of the first group received the drugs of the first line during 6 months; the intensive phase was prolonged up to 8 months by reason of advanced TB process in 20.3%; it was prolonged up to 12 months in 8.6% of patients. Limited MDR TB forms without destruction were observed in 2.9% of cases, therefore, those children and adolescents received their treatment with anti-TB drugs of the 2nd line during 4 months. The intensive phase was conducted under clinics conditions in 100% of cases.

The treatment effectiveness was determined by sputum smear conversion, sputum negativation and closing of destruction lung cavities. The sputum smear conversion took place in 100% of patients in both groups. Among patients taken the anti-TB drugs of the 2nd line (Group I) sputum smear conversion took place in 39.6% 1 month later, in 17.2% 2 months later, in 4.2% 3 months later and in 1.3% of patients with advanced processes 4 months later. In patients of the Group 2 (received the drugs of the 1st line) smear sputum conversion took place in 50.0% of cases, among remained patients it did 3 months (25.0%) and 4 months (25.0%) of treatment with anti-TB drugs of the 1st line.

The sputum negativation in children and adolescents treated with anti-TB drugs of the 2nd line (Group 1) took place in 100.0%. In 49.1% of patients negativation was marked in 49.1% of patients 1 month later, it did in 36.4% 2 months later, in 7.0% 3 months later, in 5.2% 4 months later, and in 2.3% of cases 5 months later. Among patients treated with anti-TB drugs of the 1st line sputum negativation was marked during 2nd (20.0%) and 3rd months (40.0%), it did among remained patients during 4th and 5th month (by 30.0%) relatively.

The destruction cavity closing in patients of the Group 1 was observed in 20.3%, during 6th month of treatment, in 5.8% during 4th month, in 4.3% during 8th months, and in 1.4% of cases in 10th month. In 68.2% of patients treated with anti-TB drugs of the 2nd line cavity closing did not occur that was of evidence of untimely administration of adequate treatment for children and adolescents with MDR TB. In 14.4% of patients of the Group 2 cavity closing occurred during 4th month, in 25.7% during 6th month, in 15.9% during 8th month, and in 10.2% during 10th month. Cavities closing did not occur in 33.8% ($P=0.096$).

Analysis of treatment effectiveness in children and adolescents with MDR TB reliably confirms the suggestion that this category of patients' needs in the adequate therapy. Prolongation of the treatment duration for patients with drug resistance stated to the drugs of the 1st line leads to the cure process delaying, its chronization and emergence of the adverse toxic effects.

In-patient treatment regimen, both in the intensive and continuation phases, was implemented for the majority of children and adolescents of both groups due to the great residual consequences, bad tolerance of the anti-TB drugs and poor social and living conditions in their families.

By data of the dynamic observation of in-patient and sanatorium regimens of patients of the groups 1 and 2 it is necessary to mark the more prolonged staying in clinic of patients of the group 2, more frequent emergence of toxic reactions on anti-TB drugs taking and later terms of sputum smear conversion and negativation. It leads to conclude that the timely administration of the adequate treatment with anti-TB drugs of the second line, despite of the positive dynamics obtained through treatment with anti-TB drugs of the first line (group 2) could favor to earlier and qualitative cure from MDR TB.

Treatment in the continuation phase was conducted under sanatorium conditions for 15.9% of children and 2.5% of adolescents. Only 17.4% of children and 12.5% of adolescents were treated under out-patient conditions.

All the patients after discharge from clinics were observed by phthisio-pediatricians 2 times a year. At the positive clinical and laboratory and roentgenological dynamics they were removed from dispensary notification register (23).

The dynamic observation after children and adolescents with MDR TB treated with anti-TB drugs of the 2nd line showed that the effective treatment was marked in 92.8% of cases including outcome "treatment completed" which was stated in 17.4% of patients, and the outcome "cured" was registered in 75.4% of cases with positive sputum smears. One adolescent with MDR TB (1.4%) died by reason of the concomitant pathology in term of diabetes mellitus. Treatment failure was stated in 5.8% of children and adolescents, further they were transferred to be treated with anti-TB drugs of the 3rd line.

Thus, analysis of treatment course in patients treated with drugs of the second line showed that outcomes were favorable, i.e. without exacerbations or relapses, in 92.8%.

Among children and adolescents treated with the drugs of the 1st line the effective treatment was marked in 91.3% of cases. Outcome "treatment completed" was determined in 67.5% of patients, and out of the number of sputum smear positive cases outcome "cured" was registered in 23.8%. Five (6.2%) of children and adolescents with MDR TB died because of generalized process and polyorganic insufficiency and presence of variety of concomitant pathologies ($P \leq 0.001$). Treatment failure was stated in 2.5% of children and adolescents, further they were transferred to be treated with the drugs of the second line.

TB relapse emerged in 12.5% of children and adolescents treated with the drugs of the 1st line (Group 2). Treatment completed it occurred in 3.8% 6 months later, in 2.5% one year later, and in 6.3% two years later.

It should be conclude that, despite of the continued treatment with DFL under clinic and further sanatorium conditions of the patients of the group 2 outcomes of treatment were lesser effective compared with patients of the group 1. Thus, in the group 2 6.3% of patients died while among patients of the group 1 1.4%, and later in this group of patients observed relapses of MDR TB disease were absent contrary to the group 2.

Further, analysis of effectiveness of treatment of children and adolescents with MDR TB reliably proved the importance of timely and adequate treatment administration in this category of patients. Prolongation of treatment course with DFL in patients with potential resistance to them leads to delay the cure process, its chronization and emergence of the adverse toxic responses and, also, to form the great residual changes in lungs; it can led to emerge the disease relapses in older ages. In future clinical investigations on evaluation of MDR TB treatment regimens for children and adolescents should be continued. The clinical investigations in the field of MDR TB treatment are rather necessary not only for determination of the optimal drugs combinations and terms of the therapy, but for diminishment of the adverse reactions.

Conclusion

- In the group of patients treated with anti-TB drugs of the 2nd line TB contact was stated in 71.0% of cases, at this in 63.7% it was with a patient with MDR TB, and it was not found-out in 29.0% only. In the group 1 of patients treated with anti-TB drugs of the 2st line TB contact was stated in 47.5% of cases including those with MDR TB patient in 26.1%, while it was not revealed in 48.8% of cases. I.e. children and adolescents of the Group 1 had the continued and durable contact with sputum smear positive patients in the majority of cases.

- TB of the primary genesis occurred more frequently among patients which were treated with anti-TB drugs of the 1st line while its secondary forms were mainly revealed among patients treated with anti-TB drugs of the 2nd line.
- The frequency of complications was lesser expressed among patients observed treated with anti-TB drugs of the 1st line: thus, bronchial TB was diagnosed in 63.0% and 11.2% of patients relatively, TB pleurisy occurred in 35.0% and 11.2%, and hemorrhage, tissue destruction and atelectasis in children were stated in 26.0%, 2.0% and 9.0% of patients treated with the drugs of the 2nd line relatively.
- Patients with positive sputum smear among those treated with the drugs of the 2nd line were marked by 2 times more (62.3%) than those among children and adolescents treated with the drugs of the 1st line (30.0%) ($P \leq 0.05$).
- Destructive processes in patients treated with the drugs of the 2nd line were found out in 81.2% of cases, and among those which continued the treatment with the drugs of the 1st line destruction cavities were revealed in 28.2% of cases. Therefore, children and adolescents differed significantly by pathomorphism of their disease.
- Analysis of treatment outcomes in children and adolescents of both groups showed that in 91.3% and 92.8% of cases outcome of disease was favorable. Relapse of disease emerged in 12.5% of children and adolescents treated with the drugs of the 1st line that also, confirmed the necessity of administration of the drugs of the 2nd line to the children and adolescents with MDR TB.

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