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METHOD OF OPTIMIZATION OF TARGETED THERAPY IN PATIENTS WITH GIST GENERALIZED FORM

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ABSTRACT

The purpose of this study: assess the immediate effectiveness, analyze the spectrum of side effects, study the possibilities of optimizing target therapy for patients with generalized forms of GIST based on monitoring the concentration of active metabolites of imatinib mesylate in patients' blood plasma.

Materials and methods: 23 patients with GIST who received targeted imatinib therapy were used to determine the drug's therapeutic concentration level of 1100 ng/ml [link] in the blood plasma by high performance liquid chromatography with tandem mass spectrometry detection (HPLC-MS-MS). All the patients received imatinib therapy in therapeutic regimen with daily intake 400 mg. Within the framework of study before the therapy all the patients underwent the test where the imatinib concentration in blood plasma was estimated using the High-performance liquid chromatography-tandem mass spectrometry method. When the concentration in blood was within the framework of the therapeutic range the revive studies were not carried out. In cases of reduced concentration of imatinib the dose adjustment with subsequent imatinib concentration check was made.

Results and Discussion: Among the patients receiving imatinib in therapeutic regimen with daily intake of 400 mg imatinib active metabolites concentration in blood of 9 (39.1%) patients did not reach the therapeutic level (was less than 1100 ng/ml), in blood of 14 (60.9%) patients was higher than 1100ng/ml (ranging from 1125 to 2584 ng/ml). Imatinib daily intake was escalated to 600 mg for patients whose imatinib concentration in blood at presentation (one month from first imatinib intake) was within the range from 800 to 1099 ng/ml. Daily intake increase to the highest possible recommended amount (800 mg) for 6 (26.1%) patients was determined by the results reflecting at presentation the lowest imatinib concentration in blood – from 0 to 799 ng/ml. Partial effect in terms of size/quantity reduction of metastatic foci was observed among 10 out of 23 (43.5%) patients. Stabilization took place among 9 out of 23 patients (39.1%). Therefore overall efficiency (PE+St) made 82.6% (19/23 patients). Progression was discovered among 4 (17.4%) patients.

Conclusions: In this study for the first time in Russian Federation a possibility of optimization an effective application of imatinib targeted therapy for disseminated forms of GIST was shown. In case of reduced imatinib concentration in blood intake adjustment led to targeted therapy efficacy improvement.

Keywords: gastrointestinal stromal tumor, targeted therapy, imatinib.

Introduction. Practical application of new approaches in diagnosis (based on present knowledge in molecular biology), immune histochemical tests and also the development of targeted therapy have allowed developing an effective algorithm of treating patients with mesenchymal gastrointestinal tumors.

Gastrointestinal stromal tumors (GIST) are the most commonly encountered gastrointestinal sarcomata which were singled out from the group of mesenchymal gastrointestinal tumors for a variety of clinical and morphological features [1, 8, 15, 18].

The degree of GIST incidence is 10-20 cases per population of 1000 000 per year. In the USA 5000-6000 new cases of such diseases are registered every year. GIST morbidity is equal in different geographical regions and among different ethnical groups [4]. Most of GIST develops at the age of 50-70. At any age GIST morbidity is equal among male and female [14].

Experience of application systemic chemotherapy for curing this group of tumors displayed poor result. Neither most commonly used combination MAID nor Dacarbazine and Doxorubicine monochemotherapy were effective: according to different authors the level of response was from 0 to 27% and median overall survival reached only 14-18 months [6].

According to the literature review 80% of stromal tumors have KIT mutations (exons 9, 11, 13, 17), 3-18% - PDGFRA mutations (exons 12, 14, 18) and in 12-15% of the cases of GIST KIT and PDGFRA mutations are absent (wild type genes WT) [3,5,7,14].

Imatinib has been successfully used in curing GIST since 2001 as it is a medicament of neoadjuvant and adjuvant therapy and it is a first line drug for unresectable and/or metastatic GIST.

In some cases the effectiveness of treating patients with GIST is decreasing due to the current problem of progressing drug resistance. Although only 15% of patients with GIST have intrinsic imatinib resistance and its intolerance [11], the disease of the majority of patients who initially had response to the targeted therapy is advancing as a result of acquired resistance [13]. However, in a number of cases the reason of GIST advancing is not an acquired resistance but factors that prevent long-lasting and continuous imatinib intake such as noncompliance of drug therapy, pseudoprogression and other reasons (for example, gastrectomy) [17, 19]. Consequently, before moving to the second-line therapy it is reasonable to pay special attention to the factors of GIST advancing and to exclude other reasons of resistance to imatinib.

It has been demonstrated that median time to progression and overall response rate among GIST patients with active metabolites concentration less than 1100 ng/ml is statistically lower than among patients with higher rate of metabolite concentration[12].

In the majority of cases non-response and progression are attributed to the decrease of imatinib therapeutic concentration in blood plasma which can be caused either by noncompliance of drug therapy [9, 16] or by imatinib metabolism peculiarities of every individual and also by co-medication intake that effects imatinib metabolism [19, 20, 21]. Therefore monitoring of imatinib concentration in blood plasma allows the doctor to exclude possible reasons of observable changes and minimize the risks of drug self-tapering and deterioration of therapy tolerability before it is too late.

The research objective was efficacy evaluation, adverse effects spectrum analysis, investigation of possibilities for optimization of targeted therapy of patients with generalized form of GIST based on the monitoring of imatinib mesylate active metabolites concentration in patients' blood plasma.

Materials and methods. In this research we have analyzed the efficacy and attempt to individualize the treatment of 23 patients with disseminated form of GIST who were receiving medical treatment in several medical institutions: clinical site of the Oncology and Thoracic surgery Department in MONIKI n.a. M.F.

Vladimirskiy and Moscow Oncology Centre №2. All the patients had undergone previous surgical treatment. As part of complete physical examination before including the patients whose disease had progressed into this research study they went through the following tests: chest X-ray, ultrasound investigation and/or abdominal CT/MRT, esophagogastroduodenoscopy, electrocardiography and also morphological examination of postoperative material (histological processing and IHC test).

On clinical site of Central Research Laboratory of Rostov State Medical University we have conducted the estimation of imatinib concentration of therapeutic level 1100 ng/ml in blood plasma of the GIST patients who received imatinib targeted therapy. During this estimation the High-performance liquid chromatography-tandem mass spectrometry method was used.

The evaluation of treatment efficacy was conducted on the basis of dynamic changes observed after the check EGDS. Abdominal ultrasound investigation/CT/MRT were done after 3, 6, 9 and 12 months. In support of primary efficacy parameter analysis the percentage of patients with new metastatic foci was estimated. For evaluation of chemotherapy efficacy we used well known World Health Organization criteria: complete remission (complete regression) - no evidence of tumor; partial remission (decrease of tumor by more than 50%), stabilization (decrease of tumor by less than 50% or increase by no more than 25%), progression (increase of tumor by more than 25% or appearance of new foci) [19].

The evaluation of adverse effects spectrum was conducted based on patients' complaints and medical data which includes laboratory data.

The findings of the study were processed by methods of descriptive statistics. All the calculations were made with the help of analytics software packages «Statistica for Windows. Release 10.0» (STATSOFT Inc.) and SAS.

Before entering the research all the participants signed informed consent to participate in the study. The study was approved by local ethics committee of Yaroslavl State Medical University Ministry of Health of the Russian Federation.

23 patients with disseminated forms of GIST who received imatinib therapy in therapeutic regimen with daily intake 400 mg were included in this study.

The proportion of men and women was 15/8. The average age at the moment of the research was 63,1 years (age range 35,3-78,4years).

By site of primary tumor there was the following distribution: 11 patients (47,8%) had tumor in the abdomen, 7 patients (30,4%) - in small bowel and 5 patients (21,8%) - in large bowel.

The scope of prior surgery depended on the size, the site of tumor and the degree of local spread of the process (Fig.1).

As demonstrated in Fig. 1 the majority of patients (87,0%) underwent conservative surgeries.

Based on the pathomorphological research findings two histological types of GIST were observed: spindle-sell - 82,6% (19 patients) and epitheliocellular - 17,4% (4 patients).

All the patients included in the study underwent immunohistological analysis.

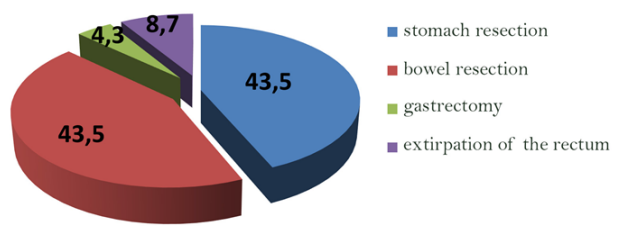

Fig.1. The scope (%) of prior surgery on patients with generalized forms of GIST

For immunohistological analysis a panel of markers including CD117, CD34, vimentin, SMA, desmin, protein S-100 and Ki67 was used. The degree of expression of immunohistological markers was rated on the scale from one to three depending on the intensity of immunohistochemical stains. GIST was diagnosed when there was a tumor cells expression of immunohistochemical marker CD117 (C-KIT). In case of doubtful reaction the presence of CD34 marker and its degree of the expression were taken into consideration. According to the carried out immunohistological analysis gene c-kit expression has been observed in 100% of the tumors. Another marker that allows to differentiate GIST, CD-34, has been observed in 78,3% of the cases which corresponds to the current data reflected in specialized literature [5].

12 (52,2%) patients with disseminated forms of GIST underwent genetic mutation analysis. In 11 (91,7%) cases c-kit gene mutation was identified and in 1 case (8,3%) PDGFRA gene mutation was identified. C-kit exon 11 mutations were identified in 8 (72,7%) cases and C-kit exon 9 mutations - in 3 (27,3%) tumors. The only PDGFRA gene mutation settled in exon 18.

The distribution of metastatic foci depending on the localization was the following: in most cases metastasis settled in liver: solitary lesion of liver was in

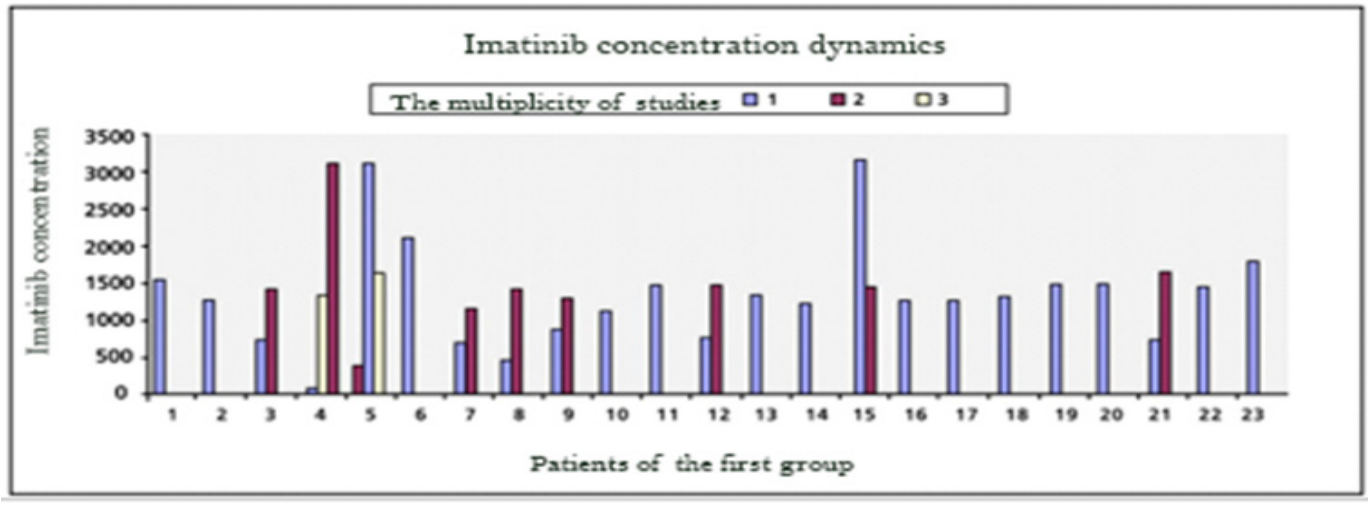

Fig. 2. Imatinib concentration in blood plasma of patients with disseminated forms of GIST

52,2% (12 patients), coexistent with peritoneum affection - in 17,4% (4 patients). Secondary peritoneum changes were observed in 26,1% (6 patients). Metastatic foci in retroperitoneal lymph nodes were identified in 4,3% (1 patient).

All the patients received imatinib therapy in therapeutic regimen with daily intake 400 mg. Within the framework of study before the therapy all the patients underwent the test where the imatinib concentration in blood plasma was estimated using the High-performance liquid chromatography-tandem mass spectrometry method. At the drug concentration in the blood corresponding to the framework of the therapeutic range, repeated studies were not conducted. In cases of reduced concentration of imatinib dose adjustment with subsequent imatinib concentration check was made.

In Fig. 2 the total amount of carried out researches on imatinib concentration in GIST patients' blood plasma and also frequency of examining imatinib detection and concentration in blood of all the 23 patients of this group are reflected.

Results and Discussion. Among the patients receiving imatinib in therapeutic regimen with daily intake 400 mg imatinib active metabolites concentration in blood of 9 (39,1%) patients did not reach the therapeutic level (was less than 1100 ng/ml), in blood of 14 (60,9%) patients was higher than 1100ng/ml (ranging from 1125 to 2584 ng/ml).

The range of imatinib active metabolites concentration discovered during the study is reflected in Fig. 3.

The decision of individualizing the therapy was made according to the results of primary study of imatinib concentration in blood. Imatinib daily intake was escalated to 600 mg for patients whose imatinib concentration in blood at presentation (one month from first imatinib intake) was within the range from 800 to 1099 ng/ml.

Daily intake increase to the highest possible recommended amount (800 mg) for 6 (26,1%) patients was determined by the results reflecting at presentation the lowest imatinib concentration in blood – from 0 to 799 ng/ml.

A month after individualizing the therapy patient subgroup with lowest imatinib concentration at presentation had a follow-up test of imatinib concentration in blood. The following results were obtained: 5 (55,6%) patients had the level of imatinib concentration higher than 1100 ng/ml, concentration of 4 (44,4%) patients continued to be lower than the therapeutic level. During the analysis and possible causes of imatinib concentration decrease identification it was discovered that 2 out of 4 patients had c-kit exon 9 mutation while other two patients independently reduced their daily intake to 400 mg due to the pharmacoeconomic difficulty of community-based drug reimbursement. After cause of imatinib concentration decrease identification patients' daily intake was increased.

The data concerning imatinib therapy success rate are presented in Table №1.

As it appears from Table 1 partial effect in terms of size/quantity reduction of metastatic foci was observed among 10 out of 23 (43,5%) patients. Stabilization took place among 9 out of 23 patients (39,1%). Therefore overall efficiency (PE+St) made 82,6% (19/23 patients). Progression was discovered among 4 (17,4%) patients.

Based on the results of medical checkup 2 patients receiving imatinib daily intake of 400 mg were recorded to have disease progression in terms of expansion in the number of metastatic foci in liver despite achieving the therapeutic level of imatinib concentration in blood plasma. To increase efficiency and achieve objective response to therapy it was decided to increase imatinib daily intake to 800 mg for those patients. Follow-up checkups and monitoring of imatinib active metabolites concentration in blood were conducted after 1, 3 and 6 months. At the end of first month from the start of drug therapy method optimization it was recorded that these patients had trough plasma concentration increased from 200 ng/ml to 1980 ng/ml and from 420 ng/ml to 2458 ng/ml. Control study of abdominal organs (CT/MRT) showed disease stabilization among those patients: quantity, size and spissitude of metastatic foci remained constant after 3, 6 months and follow-up tests.

Adverse effects. Adverse experience connected with imatinib daily intake escalation was observed in 4 cases which made 17,4% of all the patients. 3 patients (13,04%) whose daily intake had been escalated to the highest possible recommended amount (800 mg) complained of temporary swelling and asthenia which did not require drug therapy correction. Moreover, these adverse effects did not require imatinib daily intake reduction due to their not-critical intensity.

Efficacy of imatinib targeted therapy for patients with disseminated forms of GIST

Therapy efficacy	Number of patients	
	Absolute value	Relative value, %
Partial effect (PE)	10	43,5
Stabilization (St)	9	39,1
Progression (Pr)	4	17,4
Overall	23	100

Discussion. In this study we present preliminary evidence of personalised therapy efficacy evaluation among patients with disseminated forms of GIST who have been receiving imatinib treatment.

For the first time in Russian Federation test on imatinib concentration in blood plasma by High-performance liquid chromatography-tandem mass spectrometry method was carried out among GIST patients who received imatinib targeted therapy. We have not found any data using this method with solid tumors in available professional literature. At the present day an attempt to reasonably adjust imatinib daily intake on the basis of its concentration in blood was made for the first time. In case of reduced concentration (lower than the therapeutic level of 1100 ng/ml) intake adjustment was made by titering. Due to the use of this method partial effect in terms of size/quantity reduction of metastatic foci was achieved among 10 out of 23 (43,5%) patients. Stabilization took place among 9 out of 23 patients (39,1%). Therefore overall efficiency (PE+St) made 82,6% (19/23 patients). Drug tolerance was acceptable. Such approach can be a first step in personalized GIST therapy development.

Conclusions. In this study for the first time in Russian Federation a possibility of optimization an effective application of imatinib targeted therapy for disseminated forms of GIST was shown. In case of reduced imatinib concentration in blood intake adjustment led to targeted therapy efficacy improvement.

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THE IMPLEMENTATION OF LIQUID-BASED CYTOLOGY TO IMPROVE DIAGNOSTICS OF CERVIX UTERUS DISEASES

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ABSTRACT
A comparison of cytological results obtained by the method of liquid-based (LBC), implemented in practice on the basis of the laboratory of pathology, histology and cytology of the Clinic of MI M.K. Ammosov NEFU, and the traditional method is done.
It has been confirmed that the diagnostic value of the liquid-based cytology method in the diagnosis of cervical pathology is generally higher compared with TM. It is recommended to supplement the cytological study with a molecular method for the detection of human papillomavirus (HPV testing), which will improve diagnosis and subsequent treatment.
Keywords: cervical cancer, diagnostics, liquid-based cytology, screening.