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Change of concentration of biochemical markers of dysfunction of endothelium at intake of inhibitors of tyrosinekinase of I and II generations at patients with a chronic myeloid leukemia as risk factor of development of cardiovascular complications

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Aim. Identification of interrelation of endothelial dysfunction at patients with chronic myeloid leukemia (CML), the accepting inhibitors tyrosine of kinases (TKI) I and the II generations (TKI1 and TKI2 respectively), and development of arterial hypertension.

Material and methods. Examination of 137 patients with CML in the chronic phase (CP) is conducted, the median of age — 47 years. 24 of them were with for the first time the verified diagnosis of CML and earlier did not accept TKI, they have made group of control. Other patients accepted TKI: 39 patients — imatinib 400 mg/day, 36 — dasatinib 100 mg/day, 38 — nilotinib 800 mg/day) more than 6 months. In biochemical analysis of blood indicators of lipidic range were defined. Level detection of ET-1 and VEGF was made by means of enzyme immunoassay. To all patients measurement of the heart rate (HR) and the arterial blood pressure (ABP) on both hands at an interval of 2 minutes from previous was once taken.

Results. In group of patients from CML accepting nilotinib authentically significant increase in levels of systolic and diastolic ABP ($p < 0,001$) in comparison with group of control, with group of the patients accepting imatinib and dasatinib is noted. The most serious changes of lipidic range are noted at the patients accepting nilotinib. In all groups statistically significant increase in level of C-reactive protein, fibrinogen, homocysteine, endothelin-1 and VEGF in comparison with group of control is revealed. The most expressed changes are found in group of the patients accepting nilotinib, values of parameters of C-reactive protein, fibrinogen, homocysteine, endothelin-1 and VEGF are changed authentically ($p < 0,001$) and statistically significantly differ in comparison with group for the first time of the revealed patients with CML and groups of reception of imatinib and dasatinib.

Conclusion. As a result of the conducted research endothelium variation of a function at patients from CML accepting TKI1 and TKI2 is revealed. The above-stated indicators can be used as additional diagnostic criteria for assessment of risk of development of arterial hypertension in patients with CML at reception of TKI.

Key words: chronic myeloid leukemia, cardiotoxicity, endothelial dysfunction.

Relationships and Activities: none.

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Изменение концентрации биомаркеров дисфункции эндотелия при приеме ингибиторов тирозинкиназы I и II поколений у пациентов с хроническим миелолейкозом как фактор риска развития сердечно-сосудистых осложнений

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Цель. Выявление взаимосвязи эндотелиальной дисфункции у пациентов с хроническим миелоидным лейкозом (ХМЛ), принимающих ингибиторы тирозинкиназы (ИТК) I и II поколений, и развитием артериальной гипертензии.

Материал и методы. Проведено обследование 137 больных ХМЛ в хронической фазе (ХП) (средний возраст — 47 лет). Контрольную группу составили 24 пациента с впервые выявленным ХМЛ, еще не начавшие получать лечение. Остальные пациенты принимали ИТК более 6 месяцев: 39 пациентов — иматиниб 400 мг/сут, 36 — дазатиниб 100 мг/сут, 38 — nilotinib 800 мг/сут. В биохимическом анализе крови определялись показатели липидного спектра. Определение уровня эндотелина-1 (ЭТ-1) и фактора роста эндотелия сосудов (VEGF) производили с помощью иммуноферментного анализа. Всем пациентам было проведено однократное измерение частоты сердечных сокращений (ЧСС) и артериального давления (АД) на обеих руках с интервалом в 2 минуты от предыдущего.

Результаты. В группе пациентов с ХМЛ, принимавших nilotinib, отмечено статистически значимое повышение уровней систолического и диастолического АД ($p < 0,001$) по сравнению с группой контроля, а также с пациентами, принимавшими иматиниб и дазатиниб. Наиболее серьезные изменения липидного спектра отмечались у пациентов, принимавших nilotinib. Во всех группах было выявлено статистически значимое повышение уровня С-реактивного белка, фибриногена, гомоцистеина, ЭТ-1 и VEGF по сравнению с группой контроля. Наиболее выраженные изменения были обнаружены в группе пациентов, принимавших nilotinib. Так, в данной группе значения С-реактивного белка, фибриногена, гомоцистеина, ЭТ-1 и VEGF статистически значимо отличались от таковых в контрольной группе и группах с пациентами, принимавшими иматиниб и дазатиниб.

Заключение. У пациентов с ХМЛ, принимающих ИТК I и II поколений, выявлено нарушение функции эндотелия. Вышеописанные показатели могут быть

использованы как дополнительные диагностические критерии для оценки риска развития артериальной гипертензии у пациентов с ХМЛ при приеме ИТК.

Ключевые слова: хронический миелоидный лейкоз, кардиотоксичность, эндотелиальная дисфункция.

Отношения и деятельность: нет.

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Within the last decades there was progress in treatment of oncological pathology, the amount of drugs for anticarcinogenic therapy which are aimed at the alarm ways connected with cellular proliferation has increased (for example, inhibitors of tyrosinekinase (TKI)). Thanks to modern chemotherapy, the considerable results concerning duration and quality of life of patients [1] are achieved. However, modern anticarcinogenic therapy leads to serious side effects, in particular from cardiovascular system — to cardiotoxicity, which can be shown by development of arterial hypertension, disturbances of rhythm, heart failure, changes on ECG, dysfunction of left ventricle [2-5].

The chronic myeloid leukemia (CML) represents the myeloproliferative new growth caused by activation of oncogene of BCR-ABL1 [6]. Frequency of CML increases with age and by estimates in the Russian Federation is 0,7 cases on 100 people [7]. TKI are basis of treatment of CML [8]. In the first line and the subsequent therapy use imatinib, nilotinib and dasatinib; bosutinib is shown for patients with resistance or intolerance to the previous therapy of TKI. Ponatinib is used at patients with mutation of T315I or at other mutations for which there is no other therapy of TKI [9]. Significant progress in development of TKI has led to increase in life expectancy and to improvement of quality of life of patients [1]. However, an important place is given to the development of adverse events (AEs) and comorbidity during therapy.

Safety of therapy is important for sick CML at constant uses of TKI that it is connected with requirement of continuous treatment [10]. In spite of the fact that the majority of AEs initially arise at early stage of treatment, emergence of some adverse events including clinically significant cardiovascular and metabolic, it is possible months or even years later has begun therapies [11]. The median of age, sick CML in the Russian Federation makes 49 years therefore these patients can have associated diseases and risk factors which increase probability of the mediated toxicity TKI during prolonged treatment [12].

Dysfunction of endothelium to which leads oxidizing stress and inflammation is the pathophysiological cornerstone of development of the majority of cardiovascular diseases: the permeability of vascular wall for lipoproteins changes, there is activation of molecules of adhesion of leukocytes and moving of leukocytes to arterial wall [13]. Reduction of products and/or availability of nitrogen oxide (NO) and also imbalance between the vasodilators and vasoconstrictors developed by endothelium is characteristic of development of endothelial dysfunction [14]. On model of endothelium of rats, it is shown that increase in NO, endothelin-1 (ET-1) and other inflammatory markers can be induced by hyperhomocysteinemia [15]. Homocysteine is minor product of numerous biological processes in human body and, being raised, can be connected with heavy atherosclerosis and thrombotic occlusion [16]. ET-1 is the most powerful vasoconstrictor identified today, making extremely strong reduction of number of blood vessels of mammals of *in vitro*, including arteries and veins of the person [17]. The vascular endothelial growth factor (VEGF) has pro-angiogenic activity and also increases permeability of vessels and is necessary in human body for forming and maintenance of endothelial permeability [18].

However, the problem of diagnostics of endothelial dysfunction as predictor of arterial hypertension at oncohematological patients remains poorly studied that is of special interest for scientists.

Purpose of the study. To reveal interrelation of endothelial dysfunction at patients with CML, the accepting TKI I and the II generations, and development of arterial hypertension.

Material and methods

Examination of 137 patients with CML in chronic phase aged from 30 till 50 years on the basis of hematology unit of clinic of Samara State Medical University, the Institute of Experimental Medicine and Biotechnologies Samara State Medical University,

Almazov National medical research center of the Ministry of Health of the Russian Federation. The diagnosis of CML (ICD X C92.1 code) has been established according to the recommendations of the European Society LeukemiaNet (2013) on the basis of results of clinical laboratory researches and detection of Ph-chromosome and/or gene of BCR-ABL [19]. On the basis of the above-stated criteria also the disease phase has been established.

Inclusion Criteria:

1. Patients with Ph-positive chronic myeloid leukemia in chronic phase prior to treatment or the accepting inhibitors of tyrosinekinase of I (TKI1) imatinib and the II (TKI2) generations (dasatinib, nilotinib).

2. Existence of the informed consent of the patient to participation in research.

3. Patients aged 30 to 50 years.

Exclusion Criteria:

1. Acute disorder of cerebral circulation within 6 months before inspection.

2. The postponed myocardial infarction.

3. Existence of diabetes mellitus of I, II types.

4. Existence of chronic disease of kidneys of the I-V stage

5. Existence of coronary heart disease with its clinical manifestations (the II-IV functional class).

6. Existence of idiopathic hypertension of the III degree prior to therapy of TKI.

7. Existence of other oncological diseases.

8. Inflammatory diseases in aggravation stage.

The number of men has made — 64 (47%), women — 73 (53%). The median of age of patients has made 47 years (30-50). All patients have been divided into four groups. 39 patients accepting imatinib in dose of 400 mg/day have entered into the first group; in the second — 36 patients accepting dasatinib in dose of 100 mg/day; in the third — 38 patients accepting nilotinib in dose of 800 mg/day; in the fourth (group of control) — the patients with for the first time the revealed diagnosis of CML who have not begun to accept TKI. The median of reception of TKI has made $25 \pm 5,84$ months.

At all patients the anamnesis of course of disease, its duration, duration of reception of TKI in detail became clear. For calculation of the index of body weight (BMI) growth and weight was measured. To all patients routine researches were carried out: the bulk analysis of blood (BAB) on Sysmex KX-21N hemanalyzer (Roche Diagnostics, Switzerland), the biochemical analysis of blood including research of lipidic range, markers of system inflammation — the C-reactive Protein (CRP), fibrinogen, markers of endothelial dysfunction — homocysteine, endothelin-1 (ET-1), angiogenesis marker — vascular endothelial growth factor (VEGF). Level detection of ET-1 and VEGF was made by means of enzyme immunoassay. For definition of ET-1 set (BIOMEDICA GRUPPE) for quantitative definition of human big endothelin (1-38) in blood serum,

measurement range has been used: 0,02-3 pmol/L. The VEGF level was determined by set (eBioscience) for quantitative definition of human soluble receptor of 1 vascular endothelial growth factor (sVEGFR1) in serum samples by method of enzyme immunoassay.

To all patients measured the heart rate (HR). Measurement of the arterial blood pressure (ABP) was taken once by means of the auscultatory sphygmomanometer on both hands, repeated measurement of the ABP was taken in 2 minutes from previous.

The data obtained during the research processed, using the standard Microsoft Excel program and package of the certified SPSS 13.0 and Stat Soft Statistica 6.1 programs, the following mathematical-statistical methods have been applied: Kolmogorov-Smirnov's criterion for assessment of normality of distribution of values, standard descriptive statistics (average, standard error of average, median, minimum, maximum), non-parametric Mann-Whitney U-test for comparison of quantitative indices, rank correlation coefficient of Spearman's for interrelation research between quantitative characters. Distinctions considered statistically significant at $p < 0,05$ [20].

The research has been executed according to standards of appropriate clinical practice (Good Clinical Practice) and the principles of the Helsinki declaration. The study protocol was approved by the ethical committee of Samara State Medical University.

Results

The specified groups of patients have been inspected. It is most characteristic of the patients accepting nilotinib 800 mg/day there was periodic increase in arterial blood pressure (mainly in the morning). In detail clinical and demographic characteristics of sick CML are provided in table 1. In the relation of the gender and age characteristic it should be noted bigger number of women in each group, than men without statistically significant distinctions on age. Among patients in the groups receiving TKI statistically significant distinctions on BMI, duration of disease and reception of therapy of TKI were not observed (Table 1).

At the patients accepting imatinib 400 mg us statistically significant differences in the values of P_{sys} and P_{dias} , the values of the lipid profile from the control group.

In the group of patients with CML receiving dasatinib at a dose of 100 mg/day a statistically significant increase in systolic blood pressure values was found (P_{sys} $132,41 \pm 5,19$ mm Hg, $p < 0,05$) compared with the control group and the group of patients taking imatinib 400 mg/day.

Significant changes in the lipid profile were also detected: an increase in the level of VLDL ($0,72 \pm 0,08$ mmol/l, $p < 0,05$) compared with the control group and the first group, an increase in the level of TGs ($1,38 \pm 0,11$ mmol/l, $p < 0,05$) compared with the control

Table 1

Clinical and demographic parameters of patients with CML

Indicators	1st group (CML + Ima 400 mg, n=39)	2nd group (CML + Dasa 100 mg, n=36)	3rd group (CML + Nilo 800 mg, n=38)	Control group (n=24)
Sex (men/women), n (%)	18 (46) 21	17 (47) 19	18 (47) 20	11 (46) 13
Age, Me	47 [30; 50]	47 [30; 50]	48 [30; 50]	46 [30; 50]
BMI, Me±SD	25,46±3,17	26,81±4,63	26,34±4,08	24,72±4,91
Duration of disease, Me±SD, month.	42±4,36	44±4,73	47±6,28	-
Duration of therapy, Me±SD, month.	26±3,82	23±4,61	24±4,39	-
HR, per min	75,23±6,29	72,84±4,77	74,65±5,48	73,53±4,16
P_{sys} , mm Hg	127,67±6,25	132,61±6,79*/^	143,05±4,78**/^/##	124,78±5,81
P_{dias} , mm Hg	86,56±4,54	85,39±4,58	91,84±5,46**/^/##	83,23±5,15
TC, mmol/l	4,89±0,14	4,91±0,18*	6,27±0,22**/^/##	4,81±0,17
LDL, mmol/l	3,07±0,27	3,12±0,18	4,33±0,28**/^/##	3,06±0,13
VLDL, mmol/l	0,61±0,14	0,72±0,08*/^	0,92±0,17**/^/##	0,61±0,13
HDL, mmol/l	1,21±0,15	1,20±0,11	1,16±0,12**/^/##	1,19±0,07
TGs, mmol/l	1,36±0,12	1,38±0,11*	1,85±0,07**/^/##	1,33±0,08
AC	3,03±0,23	3,11±0,17*	3,94±0,27**/^/##	2,99±0,14

Notes: */**/** — significance of difference with the control group ^/^/^/ — sign imost differences compared to group 1, #/##/### — significance of differences compared with group 2. * — p<0,05, ** — p<0,001.

Abbreviations: CML — chronic myeloid leukemia, Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, BMI — body mass index, HR — heart rate, P_{sys} — systolic arterial pressure, P_{dias} — diastolic blood pressure, LDL — low density lipoproteins, VLDL — very low density lipoproteins, HDL — high density lipoproteins, TGs — triglycerides, AC — atherogenic coefficient.

Table 2

Comparative data of indicators of markers of damage of endothelium at patients with CML

Indicators	1st group (CML + Ima 400 mg, n=39)	2nd group (CML + Dasa 100 mg, n=36)	3rd group (CML + Nilo 800 mg, n=38)	Control group (n=24)
CRP, mg/ml	2,12±0,26**	3,06±0,26**/^	5,41±0,32**/^/##	1,46±0,25
Fibrinogen, g/l	3,48±0,22*	4,02±0,17**/^	4,07±0,16**/^/##	3,17±0,16
Homocysteine, μmol/l	9,53±0,31	10,80±0,39	10,93±0,28**/^	9,32±0,26
Endothelin-1, pmol/ml	0,16±0,04*	0,32±0,02**/^	0,89±0,05**/^/##	0,04±0,02
VEGF, pg/ml	54,78±7,54**	109,86±12,97**/^	165,36±11,44**/^/##	35,53±6,59

Notes: */**/** — significance of the difference with the control group, ^/^/^/ — significance of the difference in comparison with group 1, #/##/### — significance of the difference in comparison with group 2. * — p<0,05, ** — p<0,001.

Abbreviations: CML — chronic myeloid leukemia, Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, CRP — C-reactive protein, VEGF — vascular endothelial growth factor.

group and AC (3,11±0,17, p<0,05) compared with the control group.

In the group of patients with CML taking nilotinib at a dose of 800 mg/day. There was a statistically significant increasing in systolic and diastolic blood pressure levels (P_{sys} 143,21±4,78 and P_{dias} 91,84±5,46 mm Hg, p<0,001) compared with the control group with a group of patients taking imatinib 400 mg/day and dasatinib 100 mg/day. The most serious changes in laboratory parameters were also noted in the group of patients taking nilotinib 800 mg/day. In the group of patients with CML receiving nilotinib at a dose of 800 mg/day, a statistically significant increase in total cholesterol (6,27±0,22 mmol/l, p<0,001), LDL (4,33±0,28 mmol/l, p<0,001), VLDL (0,92±0,17 mmol/l, p<0,001), TGs (1,85±0,07 mmol/l, p<0,001), AC (3,9±0,27, p<0,001), a statistically

significant decrease in HDL (1,16±0,12 mmol/l, p<0,001) in comparison with control groups, patients taking imatinib 400 mg/day, patients taking dasatinib 100 mg/day.

Data on studying of markers of damage of endothelium are in detail provided in table 2.

It should be noted that a statistically significant increase in CRP, fibrinogen, homocysteine, ET-1 and VEGF levels was found in all groups of patients with CML treated with ITK compared with the control group. The most explicated changes were found in group 3 patients, the parameters of CRP, fibrinogen, homocysteine, ET-1 and VEGF changed significantly (p<0,001) and statistically significantly different compared with the control group, 1 and 2 groups. Changes in the content of biochemical markers reflect

Table 3

Correlation interrelations between markers of lipidic range and markers of damage of endothelium

Indicators	Drug	Homocysteine, $\mu\text{mol/l}$	Endothelin-1, pmol/ml	VEGF, pg/ml
TC	Ima400	0,92***	0,54***	0,96***
	Daza100	0,83***	0,49**	0,84***
	Nilo800	0,61***	0,67***	0,22
LDL	Ima400	0,67***	0,45**	0,62***
	Daza100	0,31*	0,38*	0,35**
	Nilo800	0,43**	0,39*	0,81***
VLDL	Ima400	0,80***	0,36*	0,77***
	Daza100	0,82***	0,28	0,81***
	Nilo800	0,88***	0,94***	0,28
HDL	Ima400	0,88***	0,63***	0,92***
	Daza100	0,84***	0,51***	0,89***
	Nilo800	0,87***	0,94***	0,36**
TGs	Ima400	0,94***	0,58***	0,98***
	Daza100	0,93***	0,59***	0,98***
	Nilo800	0,97***	0,93***	0,43**
AC	Ima400	0,92***	0,57***	0,95***
	Daza100	0,92***	0,58***	0,98***
	Nilo800	-0,02	0,92***	-0,14

Notes: * — $p < 0,05$, ** — $p < 0,01$, *** — $p < 0,001$.

Abbreviations: Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, VEGF — vascular endothelial growth factor, TC — total cholesterol, LDL — low density lipoproteins, VLDL — very low-density lipoproteins, HDL — high density lipoproteins, TGs — triglycerides, AC — atherogenic coefficient.

Table 4

Correlational interrelation between markers of endothelial damage and values of P_{sys} and P_{dias}

Indicators	Drug	Homocysteine, $\mu\text{mol/l}$	Endothelin-1, pmol/ml	VEGF, pg/ml
P_{sys}	Ima400	0,96***	0,57***	0,98***
P_{dias}		0,82***	0,44**	0,85***
P_{sys}	Daza100	0,75***	0,62***	0,77***
P_{dias}		0,93***	0,66***	0,96***
P_{sys}	Nilo800	0,76***	0,84***	0,31*
P_{dias}		0,90***	0,83***	0,42**

Abbreviations: Ima 400 mg — imatinib at a daily dose of 400 mg, Dasa 100 mg — dasatinib at a daily dose of 100 mg, Nilo 800 mg — nilotinib at a daily dose of 800 mg, VEGF — vascular endothelial growth factor, P_{sys} — systolic blood pressure, P_{dias} — diastolic blood pressure.

Notes: * — $p < 0,05$, ** — $p < 0,01$, *** — $p < 0,001$.

endothelial dysfunction. Particularly noteworthy is the increase in CRP and ET-1 and VEGF, which reflects the unity of the inflammation process.

Correlation analysis was carried out with the purpose to reveal interrelations of indicators of lipidic range and markers of damage of endothelium at the patients accepting ITK. Close interrelations have been revealed in 1, 2 and 3 groups between indicators of lipidic range and markers of damage, among them have been chosen homocysteine, Etendotelin-1 and VEGF (Table 3).

Besides, we carried out a correlation analysis of markers of damage to the endothelium and levels of P_{sys} and P_{dias} , during which the close interrelation of indicators was revealed (Table 4).

Patients 3 groups accepting nilotinib 800 mg/day had the clinical features characterizing them as group of persons with high arterial blood pressure. In $24 \pm 4,39$ months of reception of nilotinib, patients had the arterial hypertension of 1 degree revealed at 38,42% of persons. The highest rates of lipidic profile in interrelation with markers of damage of endothelium can demonstrate development of system inflammatory process.

Thus, in all groups statistically significant correlations of indicators of lipidic range and markers of damage of endothelium have been revealed, at the same time especially significant interrelations were defined at patients from CML accepting nilotinib 800 mg a day. In the last group of patients the share of patients with arterial

hypertension, markers of endothelial dysfunction and disturbances of lipidic exchange in comparison as with other groups of patients was authentically higher.

Discussion

It is known that cardiotoxicity is one of the most dangerous AEs resulting from therapy of oncological diseases and can influence life expectancy. Minimizing of risk of the cardiovascular complications caused by different types of therapy is vital for patients. Therefore patients need to place emphasis on early detection and assessment of risks of cardiovascular diseases at purpose of drugs TKI with CML [21].

The studying of lipid profile disorders in combination with changes in the content of markers of damage to the vascular endothelium in patients with CML and hypertension is undoubtedly interesting.

Cardiovascular AEs apparently related to the peculiarities of the action of TKI. There is an opinion that the inhibition of various TKI targets contributes to their different toxicity profiles [9]. All TKI inhibit a number of kinases, but in different values. Compared with most other TKI, dasatinib has a higher inhibitory effect against the Src family kinases, the Bruton tyrosine protein kinase and the alpha receptor for growth factor platelet receptor (PDGFR α); nilotinib is a derivative of imatinib and also inhibits PDGFR and c-Kit; Bosutinib has a higher inhibitory effect against Src-family kinases; Ponatinib has a higher inhibitory effect against PDGFR α , c-Kit and VEGFR-2 [22-26].

The spectrum of potential cardiovascular and metabolic toxicity associated with TKI therapy varies from chronic pathology to potentially life threatening and includes heart failure, prolonged QT interval, arterial hypertension, thrombosis, peripheral arterial occlusive disease, hyperlipidemia, hyperglycemia [11]. So, in patients taking nilotinib 800 mg/day the highest levels of P_{sys} and P_{dias} among all groups are noted, which, probably like other adverse events, is associated with the spectrum of nilotinib inhibited kinases. The analysis of the lipid profile in patients with newly diagnosed CML and patients receiving TKI of I and II generations showed significant changes, especially in patients taking nilotinib 800 mg/day. These patients showed a statistically significant increase in total cholesterol, LDL, VLDL, TGs, a statistically significant decrease in HDL cholesterol, and, as a result, a significant increase in atherogenicity was found. Patients taking dasatinib 100 mg/day are shown less significant but statistically significant changes — an increase in total cholesterol, VLDL, TGs and AC. Such disorders of the lipid profile are consistent with literature data [11].

Arterial hypertension serves as an activator of oxidative stress, which is accompanied by tissue damage and initiates endothelial dysfunction. Endothelial dysfunction initiates further developments leading to changes in the

content of vasoactive substances, inflammatory reactions and vascular remodeling, which, in turn, leads to the pathology of target organs [27]. Currently, one of the most studied vasoactive mediators is ET-1 and VEGF, the prognostic significance of which is confirmed in blood diseases [28]. A rat's endothelial model showed that hyperhomocysteinemia can increase the levels of ET-1 and other inflammatory markers [15].

Analysis of the data obtained during the study of endothelial function revealed the following patterns: a significant change in fibrinogen and CRP levels depending on the applied TKI, also significantly changed ET-1 and VEGF, the homocysteine level was significantly different in patients taking 800 mg/day nilotinib in comparison with newly diagnosed patients with CML and patients taking imatinib 400 mg/day. However, the level of fibrinogen was within the reference values (2-4 g/l) and was slightly increased in the dasatinib group of 100 mg/day. and nilotinib 800 mg/day. The obtained data are confirmed in a study of patients with CML and in a number of other works [29]. An increase in CRP levels ($p < 0,02$) in patients with CML using hydroxurea, interferon- α and imatinib therapy is confirmed in the study of Humlova Z, et al. in 2010 [30]. According to Fossard G, et al. (2016) comparing the level of homocysteine in patients using imatinib and nilotinib, it was 13,9 $\mu\text{mol/l}$ and 12,20 $\mu\text{mol/l}$, respectively, the author did not note interconnections between the level of homocysteine and the type of cardiovascular event. However, after conducting a ROC analysis, the authors determined a homocysteine threshold of 13,95 $\mu\text{mol/l}$, which can select patients with a high risk of morbidity [31].

Data on changes in the concentration of ET-1 in the serum of CML patients in the literature have not been found. In a research by Chand R, et al. (2016) it was noted that the highest serum VEGF levels were observed in CML (1011,5 \pm 789,09 pg/ml), which indicates the maximum angiogenic potential in this disease. Another important sign was a significant decrease in the level of VEGF in the serum after treatment of CML (294,84 \pm 401,17 pg/ml, $p=0,037$). This is shown the importance of angiogenesis in the pathogenesis of hematological malignant neoplasms [32].

Identified in the course of the study, the interrelation between lipid profile indicators and endothelium damage markers reflects the unity of the inflammation process resulting from the use of a number of TKI preparations.

Before starting treatment of TKI, each patient needs to evaluate cardiovascular and metabolic risk factors, which, together with an understanding of the toxicity profiles of each TKI, will help determine the most appropriate drug. Regular monitoring and early recognition of AE during treatment will help reduce endothelio-toxicity [11], and modification of an aggressive risk factor with the onset of prophylactic

treatment can prevent undesirable cardiovascular events. Appropriate treatment choices along with the prevention and treatment of TKI-related toxicity can help prevent premature cessation of therapy and optimize long-term results in patients with CML.

The team of authors acknowledges that the study had a number of limitations, given the small sample size, a multi-dimensional analysis was not carried out. However, we found it possible to present the obtained data, since from our point of view, it is necessary to trace the association of hypertension in changes in endothelial function in patients with CML when using TKI and the development of cardiovascular complications in the patients observed. Further monitoring of patients with CML receiving TKI will allow developing tools for predicting cardiovascular events that are available

for actual clinical practice in patients with CML before prescribing or during the treatment of TKI.

Conclusion

As a result of the conducted research endothelium variation of a function at patients from CML accepting TKI1 and TKI2 is revealed. The above-stated indicators can be used as additional diagnostic criteria for assessment of risk of development of arterial hypertension in patients with CML at reception of TKI. It will promote early identification of complications from cardiovascular system that, in turn will allow to improve the forecast of course of disease and quality of life of patients.

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Литература/References

- McGowan JV, Chung R, Maulik A, et al. Anthracycline chemotherapy and cardiotoxicity. *Cardiovasc Drugs Ther.* 2017;31:63-75. doi:10.1007/s10557-016-6711-0.
- Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med.* 2016;375:1457-67. doi:10.1056/NEJMr1100265.
- Domercant J, Polin N, Jahangir E. Cardio-oncology: a focused review of anthracycline-, human epidermal growth factor receptor 2 inhibitor-, and radiation-induced cardiotoxicity and management. *Ochsner J.* 2016;16:250-6.
- Abdel-Qadir H, Ethier JL, Lee DS, et al. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. *Cancer Treat Rev.* 2017;53:120-7. doi:10.1016/j.ctrv.2016.12.002.
- Jain D, Russell RR, Schwartz RG, et al. Cardiac complications of cancer therapy: pathophysiology, identification, prevention, treatment, and future directions. *Curr Cardiol Rep.* 2017;19:36. doi:10.1007/s11886-017-0846-x.
- Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. *Blood.* 2008;112:4808-17. doi:10.1182/blood-2008-07-077958.
- Turkina AG, Novitskaya NV, Golentkov AK, et al. register of patients with chronic myeloid leukemia in the russian federation: from an observational study to an assessment of the effectiveness of therapy in clinical practice. *Clinical oncohematology.* 2017;10(3):390-401. (In Russ.) Туркина А. Г., Новицкая Н. В., Голентков А. К. и др. Регистр больных хроническим миелолейкозом в Российской Федерации: от наблюдательного исследования к оценке эффективности терапии в клинической практике. *Клиническая онкогематология.* 2017;10(3):390-401. doi:10.21320/2500-2139-2017-10-3-390-401.
- Pallera A, Altman JK, Berman E, et al. NCCN Guidelines Insights: Chronic Myeloid Leukemia, Version 1. 2017. *J Natl Compr Canc Netw.* 2016;14(12):1505-12.
- Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol.* 2017;14(3):141-54. doi:10.1038/nrclinonc.2016.139.
- Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer.* 2012;118(12):3123-7. doi:10.1002/cncr.26679.
- Steggmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia.* 2016;30(8):1648-71. doi:10.1038/leu.2016.104.
- National Cancer Institute, Surveillance epidemiology and end results. SEER stat fact sheets: chronic myeloid leukemia. Available from: <http://seer.cancer.gov/statfacts/html/cmly.html>. Accessed 12, 2020.
- Ross R. Atherosclerosis: an inflammatory disease. *Am Heart J.* 1999;138(5 Pt 2):419-20. doi:10.1016/s0002-8703(99)70266-8.
- Lai WKC, Kan MY. Homocysteine-induced endothelial dysfunction. *Ann Nutr Metab.* 2015;67(1):1-12. doi:10.1159/000437098.
- Yang RX, Huang SY, Yan FF, et al. Danshensu protects vascular endothelia in a rat model of hyperhomocysteinemia. *Acta Pharmacol Sin.* 2010;31(10):1395-400. doi:10.1038/aps.2010.167.
- Brattstrom L, Wicken DE. Homocysteine and cardiovascular disease: cause or effect? *Am J Clin Nutr.* 2000;72(2):315-23.
- Inoue A, Yanagisawa M, Takawa Y, et al. The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. *J Biol Chem.* 1989;264(25):14954-9.
- Kamba T, Tam BY, Hashizume H, et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. *Am J Physiol Heart Circ Physiol.* 2006;290(2):H560-76. doi:10.1152/ajpheart.00133.2005.
- Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood.* 2013;122(6):872-84. doi:10.1182/blood-2013-05-501569.
- Rebrova OY. Statistical analysis of medical data. Application software package STATISTICA. M.: Media Sphere, 2002. p. 305. (In Russ.) Реброва О.Ю. Статистический анализ медицинских данных. Применение пакета прикладных программ STATISTICA. M.: МедиаСфера, 2002. с.305. ISBN 5-89084-013-4.
- Dong J, Chen H. Cardiotoxicity of Anticancer Therapeutics. *Front Cardiovasc Med.* 2018;5:9. doi:10.3389/fcvm.2018.00009.
- ICLUSIG® (ponatinib). Full prescribing information. ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA; 2016.
- BOSULIF® (bosutinib). Full prescribing information. Pfizer Labs, New York, NY; 2016.
- TASIGNA® (nilotinib). Full prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2016.
- Sprycel® (dasatinib). Full prescribing information. Bristol-Myers Squibb, Princeton, NJ; 2016.
- GLEEVEC® (imatinib). Full prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2016.
- Dzau VJ, Antman EM, Black HR, et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes. Part I: pathophysiology and clinical trial evidence risk factors through stable coronary artery disease. *Circulation.* 2006;114(25):2850-70. doi:10.1161/circulationaha.106.655688.
- Davydkin IL, Kurtov IV, Khairtdinov RK, et al. Blood diseases in ambulatory practice: Manual, 2nd ed. and ext. Moscow: GEOTAR Media, 2014. p. 184 (In Russ.) Давыдкин И.Л., Куртов И.В., Хайретдинов Р.К., Степанова Т.Ю., Гриценко Т.А., Кривова С.П. и др. Болезни крови в амбулаторной практике: Руководство, 2-е изд., испр. и доп. М.: ГЭОТАР-Медиа, 2014. с.184. ISBN: 978-5-9704-2725-5.
- Jain A, Gupta N, Singh T, Agarwal S. A Study of Haemostatic Parameters in Patients of Chronic Myeloid Leukaemia. *J Clin Diagn Res.* 2016;10(7):OC19-23. doi:10.7860/JCDR/2016/19185.8135.
- Humlová Z, Klamová H, Janatková I, et al. Changes of Immunological Profiles in Patients with Chronic Myeloid Leukemia in the Course of Treatment. *Clin Dev Immunol.* 2010;2010:137320. doi:10.1155/2010/137320.
- Fossard G, Blond E, Balsat M, et al. Hyperhomocysteinemia and high doses of nilotinib favor cardiovascular events in chronic phase Chronic Myelogenous Leukemia patients. *Haematologica.* 2016;101(3):e86-90. doi:10.3324/haematol.2015.135103.
- Chand R, Chandra H, Chandra S, Verma SK. Role of Microvessel Density and Vascular Endothelial Growth Factor in Angiogenesis of Hematological Malignancies. *Bone Marrow Res.* 2016;2016:5043483. doi:10.1155/2016/5043483.