Kirichenko Yu. Yu., Belenkov Yu. N., Privalova E. V.,
Naymann Yu. I., Gitel E. P., Novikova O. V., Ilgisonis I. S.
M. Sechenov First Moscow State Medical University, Moscow, Russia

Vasculotoxicity of Chemotherapy: Assessment of Endothelial Dysfunction Biomarkers' Levels in Gastric Cancer Patients

Aim — To evaluate dynamics of biomarkers for endothelial dysfunction (ED), including endothelin-1 (ET-1) and von Willebrand factor (VWF) in patients with stomach cancer (adenocarcinoma) before and after polychemotherapy (PCT); to compare these results with respective values in healthy volunteers and patients with cardiovascular diseases (CVD); to study correlations of the ED biomarkers with indexes of instrumental evaluation of endothelial dysfunction.

Material and methods — The study included 75 participants, including 25 healthy volunteers (control group), 25 patients with documented CVDs (arterial hypertension + ischemic heart disease), and 25 patients of the main group with histologically documented stage II-IV stomach cancer (adenocarcinoma) who received different courses of PCT with platinum-based agents (oxaliplatin, cisplatin) and fluoropyrimidines (5 fluorouracil, capecitabin). Laboratory measurement of ED biomarkers, computerized nailfold video capillaroscopy (CNVC), and finger laser photoplethysmography (PPG) (methods for noninvasive evaluation of vascular wall and ED), electrocardiography, 24-h ECG Holter monitoring, and echocardiography (EchoCG) were performed for all patients of the main group prior to PCT and within one months after the last course completion. This evaluation was performed once for healthy volunteers and patients of the CVD group upon inclusion into the study.

Results — In the main group, ET-1 levels were non-significantly lower than normal and did not change during the courses of antitumor treatment (0.95 [0.6; 1.4] and 0.94 [0.7; 1.4] pg/ml ($p<0.9$) before and after PCT, respectively). Statistically significant differences were found between the control group and oncological patients after the treatment ($p<0.04$). Levels of VWF remained within the normal range in all examined participants and did not significantly differ between study groups, including oncological patients before and after the specific treatment ($p>0.05$ for all comparisons). The correlation analysis detected significant correlations of ET-1 levels with functional disorders of microcirculation, ET-1 with the occlusion index ($r_s=0.56$; $p=0.005$), ET-1 with percentage of capillary restoration (PCR, $r_s= -0.72$; $p=0.018$) and with the incidence rate of supraventricular extrasystole ($r_s=0.48$; $p=0.032$).

Conclusion — The dynamics of ED biomarkers was studied for the first time in patients with stomach cancer receiving a specific antitumor therapy. Although no significant changes in ET-1 and VWF were observed during the PCT (probably due to exhaustion of the endothelial system and a small patient sample), these indexes can be considered as early vasculotoxicity markers due to the presence of significant correlations with indexes of impaired endothelial function according to the results of instrumental evaluation.

Keywords — Endothelial dysfunction; biomarkers; endothelin-1; von Willebrand factor; stomach cancer, polychemotherapy

For Citation — Kirichenko Yu. Yu., Belenkov Yu. N., Privalova E. V., Naymann Yu. I., Gitel E. P., Novikova O. V. et al. Vasculotoxicity of Chemotherapy: Assessment of Endothelial Dysfunction Biomarkers' Levels in Gastric Cancer Patients. Kardiologiia. 2020;60(5):35–40. [Russian: Кириченко Ю. Ю., Беленков Ю. Н., Привалова Е. В., Найманн Ю. И., Гитель Е. П., Новикова О. В. и др. Васкулотоксичность полихимиотерапии: оценка динамики уровня биомаркеров дисфункции эндотелия у больных раком желудка. Кардиология. 2020;60(5):35–40.]

Corresponding author — Kirichenko Yulia Yurjevna. E-mail: kataraza@yandex.ru

Oncological and cardiovascular diseases remain the lead causes of the morbidity and total mortality of the world's population [1]. Currently, about 33 million people live with a diagnosis of cancer worldwide, including the Russian Federation, 8.8 million of whom die annually. Stomach cancer is the sixth-most common malignant neoplasm, characterized by high mortality [2]. The development of new chemo- and radiation therapies have allowed making progress in the treatment of patients with various types of cancer, including gastrointestinal cancers, over the past several decades. For example, an effective combination of anti-cancer fluoropyrimidines and platinum agents extends the time to progression by at least 6 months, and total life expectancy by 12 months [3–5].

However, multi-agent chemotherapy (MAC) can contribute to the development of various severe and often life-

threatening conditions, particularly cardiovascular disorders (hypertension, thrombotic complications, chronic heart failure [CHF], cardiomyopathies, arrhythmias) [6–9]. In 30% of patients with cancer, cardiovascular diseases (CVDs) are the leading cause of death [10] due to the damaging effect of MAC on the structures of cardiomyocytes and endotheliocytes, with the development of severe endothelium dysfunction (ED) leading to cardiovascular toxicity. ED is the initial stage of the development of CVDs, which progresses with the remodeling of the vascular wall of large and small vessels and the continuous worsening of the cardiac pathology.

According to various authors, 5 fluorouracil (5 FU) and its pro-drug capecitabine contribute to the development of cardiovascular toxic effects in 1–68% of cases that occur more commonly within 72 hours after infusion [11]. Myocardial ischemia most commonly develops due to endotheliocyte damage with the subsequent release of endothelin-1 (ET-1), which increases the contractility of vascular smooth muscle cells and spasm of the coronary arteries even in the absence of hemodynamically significant stenosis of the coronary bed [12]. Metabolite 5-FU (fluoroacetate) also has a direct damaging effect on the endothelium through the inhibition of endothelial nitric oxide (NO) – synthase and activation of the endothelium-independent, protein kinase C – mediated vasoconstriction [13]. Cardiovascular toxic effects of platinum agents include hypertension in 14–53% of patients who receive them, thromboembolic complications in 9%, myocardial ischemia up to myocardial infarction in 3%, and cerebrovascular disorders in 2% of cases [14–16]. Their development is associated with direct endotheliocyte damage and subsequent ED, hyperaggregation of platelets, and reduction of NO bioavailability [13].

Thus, early detection of ED, especially in patients with cancer, appears to be reasonable with a view to slowing down its progression, which gave rise to the initiation and performance of this study.

Materials and Methods

The study included 25 patients with stomach cancer (treatment group), 25 healthy volunteers (control group), and 25 patients with documented CVD (hypertension + coronary artery disease [CAD]) (comparison group). The group of patients with CVDs was comparable with the treatment group (Table 1).

Patients were enrolled, blood samples were collected, and noninvasive instrumental examinations were performed in Cardiology Department No. 1, Surgical Oncology Department of University Clinical Hospital No. 1, and Department of Hospital Therapy No. 1 (N. V. Sklifosovsky Institute of Clinical Medicine, I. M. Sechenov First Moscow State Medical University). All patients of the treatment group underwent electrocardiography, echocardiography, and 24-hour Holter monitoring, computerized nailfold video capillaroscopy (NVC, Capillaroscan-1), and laser finger photoplethysmography (PPG, Angioscan-01) before and after the MAC courses to assess the functional state of the cardiovascular system and to examine the vascular wall in different parts of the vascular bed. Healthy volunteers and patients with CVDs underwent all the examinations only once during the study.

The collected blood samples (n <100) were centrifuged and frozen at –80°C to determine the levels of ED biomarkers (ET-1, von Willebrand factor [VWF]). The plasma samples were later thawed at room temperature, and the levels of VWF and ET-1 were determined by enzyme-linked immunoelectrodiffusion essay (ELIZA) using the commercial kits Technoclon and EnzoLife Scientific in the Sechenov University Interclinical Laboratory. In the group of patients with cancer, blood was collected before and after the courses of MAC, and in healthy volunteers and patients with CVDs once during the study.

The study followed the principles of the Declaration of Helsinki.

Data were processed using nonparametric methods (the Wilcoxon test and the Mann-Whitney test) in GraphPad Prism 8. The Spearman's coefficient was used in the correlation analysis. The differences between the parameters compared were considered statistically significant with $p < 0.05$.

Results

The study included 75 patients: 25 patients with histologically confirmed stage II–IV gastric cancer (adenocarcinoma) (treatment group), 25 healthy volunteers (control group), and 25 patients with the established diagnoses of hypertension + CAD (CVD group). The mean age of patients with cancer was 63.6±13.4 years old. Most of them were male. The group of patients with CVDs was comparable with the treatment group by main clinical and functional characteristics (see Table 1).

All patients in the treatment group underwent several courses of MAC, including platinum agents (oxaliplatin, cisplatin) and fluoropyrimidines (5 fluorouracil and its pro-drug capecitabine).

Evaluation of the changes in concentration of endothelial dysfunction biomarkers with time

Although the ET-1 levels were below normal in all groups, including healthy volunteers, the highest values were recorded in patients with cancer both before and after the MAC courses (Table 2). There were statistically significant differences between the control group and patients with cancer after the treatment ($p < 0.04$). The lowest levels of

ISSN 0022-9040. Kardiologiia. 2020;60(5). DOI: 10.18087/cardio.2020.5.n1069

Table 1. Clinical, laboratory, and instrumental characteristics of patients included in the study

Parameter	Treatment group (n <25)	CVD group (n <25)	Control group (n <25)	p
	1	2	3	
Mean age, years	63.6±13.4	65.5±7	54.6±10.5	p_{1-2} >0.05 p_{1-3} <0.05 p_{2-3} <0.05
Sex: M/F	17/8 (68/32)	11/14 (44/56)	11/14 (44/56)	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
BMI before/ after MAC, kg/m^2	25.87±3.52/ 22.31±5.86	30.2±6.2	27.71±4.74	p_{1-2} <0.05 p_{1-3} <0.05 p_{2-3} >0.05
Smoking	9 (36)	10 (40)	7 (28)	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
Hyper-cholesterol-lemia	9 (36)	8 (32)	11 (44)	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
Carbohydrate imbalance	3 (12)	3 (12)	0	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
Hyper-tensive heart disease	12 (48)	25 (100)	0	p_{1-2} <0.05 p_{1-3} <0.05 p_{2-3} <0.05
CAD	7 (28)	25 (100)	0	p_{1-2} <0.05 p_{1-3} <0.05 p_{2-3} <0.05
CHF	3 (12)	0	0	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
HR before/ after MAC, bpm	72 [67; 83]/ 80 [75; 87]	68 [61; 73]	68 [60; 74]	p_{1-2} <0.05 p_{1-3} <0.05 p_{2-3} >0.05
Mean BP, mmHg: SBP/ DBP before/ after MAC	140 [130; 150]/ 90 [85; 95]/ 143 [135; 155]/ 90 [85; 95]	135 [125; 145]/ 85 [75; 85]	118 [110;125]/ 80 [75; 85]	p_{1-2} >0.05 p_{1-3} <0.05 p_{2-3} <0.05
LVEF before/ after MAC, %	62 [58; 64]/ 59 [53; 65]	60 [57; 63]	61 [59; 66]	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
E/A before/ after MAC	0,9 [0.7; 1.11]/ 0,7 [0.6; 0.76]	0,7 [0.54; 0.9]	1,16 [0.8; 1.3]	p_{1-2} >0.05 p_{1-3} <0.05 p_{2-3} <0.05

The data of the treatment group are presented for the two-time points: before the MAC courses and within 1 month after the last course. The data of the control and CVD groups were collected only once during the study. The data are presented as the median [25th percentile; 75th percentile] or as the absolute and relative values; age and BMI are expressed as the mean ± standard deviation. The p-value for the intergroup differences using the chi-squared test. CVDs, cardiovascular diseases; BMI, body mass index; MAC, multi-agent chemotherapy; CAD, coronary artery disease; CHF, chronic heart failure; HR, heart rate; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction.

ET-1 were recorded in patients with CVDs (0.4 [0.2; 0.45] pg/mL); these levels differed significantly between the treatment group and the control group (p <0.0001).

VWF levels remained within the normal range in all patients studied and did not significantly differ between the groups, including patients with cancer before and after treatment (p >0.05 for all comparisons; see Table 2).

The correlation analysis identified direct correlations between the mean power of the ET-1 levels and the occlusion index (OI, rs<0.56; p<0.005; see Figure 1A) and left ventricular end-systolic volume (rs<0.52; p<0.027), an inverse relationship between ET-1 and percentage of capillary recovery (PCR, rs< – 0.72; p<0.018; see Figure 1B). Both parameters (OI and PCR) reflect the functional disorders of the microvasculature. Moreover, a significant positive correlation of the ET-1 levels with the incidence of supraventricular arrhythmia (rs<0.48; p<0.032) was found.

The correlation analysis determined trends in the presence of mean-power direct correlations of the VWF levels with resistance index (rs<0.382; p<0.07) and OI (rs<0.4; p<0.06).

Discussion

This was the first study evaluating the changes in concentrations of ED biomarkers with time in patients with stomach cancer during MAC. An additional comparative analysis of the findings for healthy volunteers and patients with documented CVDs was carried out.

The highest levels of ET-1 were recorded in the group of patients with cancer (0.95 [0.6; 1.4] and 0.94 [0.7; 1.4] pg/mL before and after the treatment, respectively) and differed significantly compared with the group of healthy volunteers (p <0.04). These findings may be indicate activation of the endothelial system caused by the adverse effects of anti-cancer agents. It should be noted that the lowest levels of ET-1 were found in patients with CVDs; these differed significantly from the values in the treatment and control groups (p <0.0001). This can probably be explained by the positive effect of optimal recommended drug therapy in patients of this group. The additional analysis revealed statistically significant positive correlations of the ET-1 levels with OI and PCR, characterizing functional changes in arterioles and capillaries (p <0.03), which is directly indicative of microvascular damages.

The levels of VWF remained within the normal range for all patients studied, including patients with cancer before and after the treatment, and did not significantly differ between the groups (p >0.05 for all comparisons). This may be due to the presence of other conditions/factors affecting these levels (autoimmune diseases, physical overwork, stress, trauma), an insufficient number of subjects, and/or a short follow-up period.

Table 2. Levels of the biomarkers of endothelial dysfunction in all study groups

Parameter	Control group (n <25)	Treatment group (n <25)		CVD group (n <25)	p
		Before MAC courses	After MAC courses		
	1	2	3	4	
Endothelin-1, pg/mL (normal range 1–3 pg/mL)	0.78 [0.6; 0.9]	0.95 [0.6; 1.4]	0.94 [0.7; 1.4]	0.4 [0.2; 0.45]	p_{1-2}<0.1; p_{1-3}<0.04 p_{1-4}<0.0001; p_{2-4}<0.0001 p_{3-4}<0.0001; p*<0.9
von Willebrand factor, IU/mL (normal range 0.5–1.5 IU/mL)	0.9 [0.8; 1.1]	0.75 [0.7; 0.9]	0.8 [0.74; 0.9]	0.9 [0.7; 1.24]	p_{1-2}<0.07; p_{1-3}<0.1 p_{1-4}<0.1; p_{2-4}<0.3 p_{3-4}<0.4; p*<0.6

The data are expressed as the median [25th percentile; 75th percentile].
p, the statistical significance estimated using the Mann–Whitney criterion; p*, the statistical significance of intragroup differences estimated using the Wilcoxon test (p <0.05). CVDs, cardiovascular diseases; MAC, multi-agent chemotherapy.

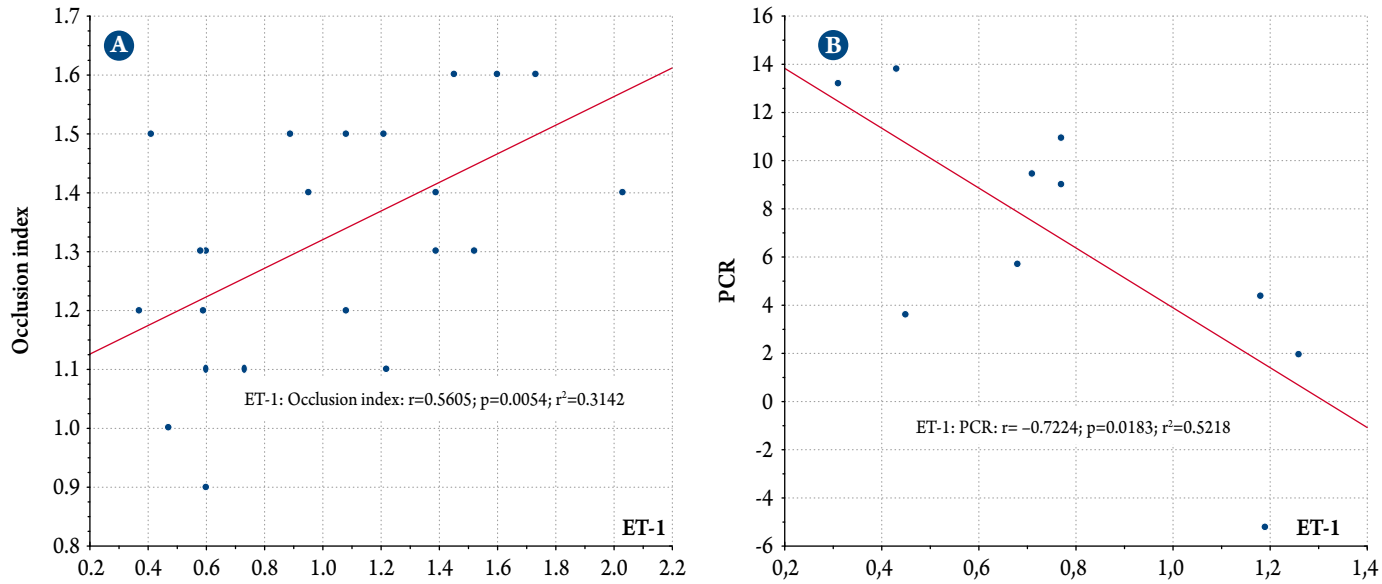
ED in patients with cancer is used as a marker of the risk of cardiovascular complications (CVCs) and closely correlates with traditional CVD risk factors in healthy patients. Thus, evaluation of endothelial function is an essential element for identifying asymptomatic patients at high risk of CVDs and stratification of risk in patients with known cardiac pathology before ordering MAC.

Currently, the primary methods for evaluating ED are laboratory assessment of the proven biomarker levels and instrumental evaluation of endothelium-dependent vasodilation. The determination of blood biomarker levels is a highly reproducible and precise method for the diagnosis of ED. However, it is of high cost, which limits its widespread use in routine practice. Interestingly, the levels of biologically active substances circulating in blood plasma depend not only on the degree of endothelial damage but also on many other factors (immune system disorders, infectious diseases, concomitant pathology, etc.). Of many ED biomarkers, ET-1, VWF, E-selectin, and P-selectin, cellular adhesion molecules (sICAM-1, sVCAM-1) were identified to have the highest predictive value for the risk of CVDs and complications.

ET-1 is the most potent of the known vasoconstrictive agents, acting through receptors ETA and ETB of two types. When ET-1 binds to receptors of one or another type, either vasoconstrictive (ETA) or vasodilative (ETB) properties manifest. The final effect depends on its concentration in the blood plasma. Thus, if a level is low, the biomarker binds mainly to ETB-receptors. In the case of ED, the levels of ET-1 increase significantly when it begins to bind to ETA-receptors of the smooth muscle cells and demonstrates its main activity by causing a pronounced vascular spasm [17]. Many authors showed ET-1 as a predictor of the development of cardiac pathology in currently healthy individuals who have traditional risk factors for the development of CVDs [18, 19].

VWF is another biomarker of ED with high predictive value. It is a blood plasma protein responsible for hemostasis.

Figure 1. The correlation of functional changes in arterioles (occlusion index; A) and capillaries (PCR; B) with ET-1 levels



ET-1, endothelin-1; PCR, the percentage of the capillary recovery.

ISSN 0022-9040. Kardiologiia. 2020;60(5). DOI: 10.18087/cardio.2020.5.n1069

It is formed mainly in endothelial cells, megakaryocytes, and subendothelial connective tissue. The increased levels of this biomarker has significantly correlated with a high risk of cardiac pathology and complications in many studies [19–22].

This study was the first time that changes in the levels of ED biomarkers have been evaluated with time in patients with stomach cancer during MAC (platinum agents and fluoropyrimidines). ET-1 and VWF levels did not exceed upper normal limits, did not change significantly in patients with cancer during the specific treatment, and did not differ statistically significantly between the study groups. This may be explained by a small sample of patients and a short follow-up period, deterioration of the endothelial system in the presence of risk factors, cancer, comorbidities, activation of antioxidant protection, and a positive effect on the endothelium of a drug therapy used by the majority of the patients studied (angiotensin-converting enzyme [ACE] inhibitors, beta-blockers, statins, antiplatelet drugs).

Conclusion

This study is the first to evaluate changes in concentrations of endothelial dysfunction biomarkers with time in patients with stomach cancer during the specific anti-cancer therapy. Although no reliable changes in the levels of endothelin-1 and von Willebrand factor were identified during multi-agent chemotherapy, these parameters can be considered as early markers of vascular toxicity due to the presence of statistically significant correlations with the instrumentally proven deterioration of endothelial function.

Funding

The study was carried out with the financial support of the Russian Fund of Fundamental Investigations as a part of project No. 1931590034.

It was supported by the Project of Improving the Competitiveness of the Leading Russian Universities among the World's Leading Scientific and Educational Centers.

No conflict of interest is reported.

The article was received on 11/01/20

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ISSN 0022-9040. Kardiologiia. 2020;60(5). DOI: 10.18087/cardio.2020.5.n1069