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ИЗУЧЕНИЕ РАСПРОСТРАНЕННОСТИ ПОЛИМОРФНЫХ ВАРИАНТОВ ГЕНОВ ФАКТОРОВ СВЕРТЫВАНИЯ КРОВИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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Цель. Изучить частоту носительства полиморфных аллельных вариантов генов факторов свертывания крови у онкологических больных.

Материалы и методы. Обследовано 213 больных с морфологически подтвержденными онкологическими заболеваниями. Исследовали образцы геномной ДНК из периферической крови больных. Методом полимеразной цепной реакции (ПЦР) в реальном времени изучали полиморфные сайты генов системы гемостаза: F2 (G20210A, rs1799963), F5 (G1691A, rs6025), F7 (G10976A, rs6046), F13 (G226A, rs5985), FGB G(-455)A (rs1800790), ITGA2-α2 (C807T, rs1126643), ITGB3-b (T1565C, rs5918), PAI-1 4G(-675)5G, rs1799889).

Результаты. Частота носительства альтернативного аллеля полиморфного локуса F2 (G20210A) в исследуемой группе составила 1,6%, F5 (G1691A) – 3,5%, F7 (G10976A) – 13,4%, F13 (G226A) – 28,2%, FGB G(-455)A – 24,9%, ITGA2-α2 (C807T) – 41,5%, ITGB3-b (T1565C) – 15,5%, PAI-1 4G(-675)5G – 56,6%. Установлено статистически значимое превышение частоты распространенности «аллелей риска» полиморфных локусов F5 G1691A ($p=0,0169$), F13 G226A ($p=0,0007$), FGB G(-455)A ($p<0,0001$) и ITGA2-α2 C807T ($p=0,0201$) у онкологических больных по сравнению с общей популяцией. В тех же локусах, за исключением ITGA2-α2 (C807T), выявлены статистически значимые различия частоты распространенности альтернативных аллелей при различных локализациях онкологического процесса. У 92,0% больных определена комбинация SNP в различных звеньях системы гемостаза.

Заключение. Учитывая высокую частоту выявления «аллелей риска» во всех звеньях свертывающей системы гемостаза, целесообразно проведение дополнительных исследований для определения необходимости добавления антиагрегантов к антитромботической терапии у онкологических больных.

Ключевые слова: *полиморфные сайты; гены факторов свертывания крови; тромботические осложнения; онкология.*

A STUDY OF PREVALENCE OF POLYMORPHIC VARIANTS OF GENES OF BLOOD COAGULATION FACTORS IN ONCOLOGICAL PATIENTS

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Aim. To study the prevalence of carriage of polymorphic allele variants of genes of blood coagulation factors in oncological patients.

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Materials and Methods. 213 Patients with morphologically confirmed oncological diseases were examined. Samples of genomic DNA of peripheral blood of the patients were examined. Using polymerase chain reaction (PCR), polymorphic sites of genes of hemostatic system were studied in real time: F2 (G20210A, rs1799963), F5 (G1691A, rs6025), F7 (G10976A, rs6046), F13 (G226A, rs5985), FGB G(-455)A (rs1800790), ITGA2-α2 (C807T, rs1126643), ITGB3-b (T1565C, rs5918), PAI-1 4G(-675)5G, rs1799889).

Results. The prevalence of carriage of alternative allele of F2 (G20210A) polymorphic locus in the studied group was 1.6%, of F5 (G1691A) – 3.5%, of F7 (G10976A) – 13.4%, of F13 (G226A) – 28.2%, of FGB G(-455)A – 24.9%, of ITGA2-α2 (C807T) – 41.5%, of ITGB3-b (T1565C) – 15.5%, of PAI-1 4G(-675)5G – 56.6%. A statistically significant increase in the frequency of 'risk alleles' of F5 G1691A ($p=0.0169$), F13 G226A ($p=0.0007$), FGB G(-455)A ($p<0.0001$) and ITGA2-α2 C807T ($p=0.0201$) polymorphic loci was found in oncological patients as compared to the general population. In the same loci, except ITGA2-α2 (C807T), statistically significant differences in the frequency of alternative alleles were found in different localizations of the oncological process. In 92.0% of patients, SNR combination was determined in different components of hemostatic system.

Conclusion. Taking into account a high frequency of identification of 'risk alleles' in all components of hemostatic system, it is reasonable to carry out additional research to determine the necessity of addition of antiaggregants to antithrombotic therapy in oncological patients.

Keywords: *polymorphic sites; genes of blood coagulation factors; thrombotic complications; oncology.*

Venous thromboembolic complications (VTEC) usually manifested as deep vein thrombosis (DVT) or thromboembolism of pulmonary artery (TEPA), are multifactorial diseases based on both acquired and genetic risk factors. In modern understanding of the pathogenesis of VTEC, a significant role is assigned to hereditary disorders in the blood coagulation system [1]. VTEC occur with age-related frequency in one to three individuals per 1000 population annually. The rate of lethal outcomes is more than 5%, mostly owing to TEPA [2]. Both genders equally suffer from the first venous thrombosis, but the risk of recurrent thrombosis is higher in males than in females [2,3].

At present of no doubt is the fact that in patients with oncological diseases VTEC are more common, and migrating venous thrombosis is a manifestation of the paraneoplastic syndrome [4]. Mechanisms of hemostasis participating in thrombogenesis, are also involved in progression of tumor, angiogenesis and metastatic spread [5]. According to different data, risk of VTEC in oncological patients is four [6] to seven and more [4] times higher than in non-oncological patients. To some estimates, 15-20% of patients with cancer suffer from DVT or TEPA [7]. In later publications 11% of cases of thrombosis are identified within a year [8], F. Horsted, et al. showed that the annual rate of VTEC makes from 0.5 to 20% depending on the kind of cancer and the background risk [9], and the study of M. Li, et al. evaluated the general incidence of VTEC in oncological patients as 2.3% [10]. Besides, cancer is an independent risk factor for recurrence of VTEC and bleedings in oncological patients [11,12].

In most publications, the connection between carriage of single nucleotide polymorphism (SNP) of genes of blood coagulation system and cancer is studied in the aspect of their influence on the risk of initiation, development and progression of tumor process. Thus, in carriers of anticoagulant variant of F13 (G226A) allele of XIII blood coagulation factor, the risk of development of colorectal

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cancer was 15% lower than in non-carriers, and procoagulant mutations of 4G(-675)5G PAI-1 plasminogen activator inhibitor gene did not influence the risk of its initiation [13]. Associations of SNR in F5 and F10 genes with the risk for development of breast cancer (BC) were shown [14]. At the same time the data of the frequency of inherited forms of VTEC in oncological patients are very scarce. It was found that in case of a combination of mutation in F5 *Leiden* gene and cancer, the risk for thrombosis increases 12-fold as compared to individuals without cancer and mutation [15]. An important problem in oncology is thromboses of rare localizations. In the presence of thrombophilia the risk of thrombosis of mesenteric veins increases 100-fold, in case of mutation in F5 (G1691A) gene the risk of thrombosis of retina increases 6-fold, and in case of mutation in F2 (G20210A) gene – 8-fold [16].

Aim – to evaluate prevalence of polymorphic allelic variants of genes of hemostatic system in oncological patients.

Materials and Methods

The study involved 213 patients including 143 women at the age of 51.89±1.12 years and 70 men at the age of 57.97±1.59 years with a morphologically verified oncological disease. All the patients were undergoing treatment in Rostov Research Institute of Oncology in the period from November 2018 to February 2019.

The candidates for study were selected using random selection method before the start of multi-course chemotherapy. All the participants signed informed consent (the study was approved by Local ethic committee).

The period of observation included four months. Distribution of tumors by localization was the following: BC – 73 (34.3%), lung cancer (LC) – 18 (8.4%), tumors of female reproductive system (TFRS) 16 (7.5%), tumors of GIT (TGIT) – 69 (32.4%), lymphomas – 15 (7.0%), others (multifocal carcinoma, tumors of the central nervous system, head and neck, bones and soft tissues) – 22 (10.3%). For comparison with the general population dbSNP data base was used developed and supported by the National Center of Biotechnological Information (NCBI) of the USA (TOPMED program) [17].

The studied material was samples of genomic DNA obtained from peripheral blood of patients. DNA was extracted using Proba-Rapid-genetika reagent kit; allelic variants of genes were determined by the method of polymerase chain reaction (PCR) in real time using CardioGenetika Thrombophilia reagent kit; the reaction was registered using DT prime 5M1 detecting amplifier (DNK-technologia, Russia). Eight polymorphic loci of genes of blood coagulation factors were used: of II coagulation factor, F2, (G20210A, rs1799963), of V factor Leiden, F5 (G1691A, rs6025), of VII factor, F7 (G10976A, rs6046), of XIII factor, F13 (G226A, rs5985), of fibrinogen, FGB G(-455)A (rs1800790), of platelet receptor to collagen ITGA2-α2 integrin (C807T, rs1126643), platelet receptor of fibrinogen ITGB3-b (T1565C, rs5918), of plasminogen activator inhibitor PAI-1 4G(-675)5G, rs1799889).

Statistical processing of the data was implemented using standard approaches of population-genetic studies, with use of Office Excel (Microsoft Corporation, USA) and STATISTICA 10.0 (Stat Soft Inc., USA) application programs The control sample was tested for correspondence with Hardy-Weinberg equilibrium by $\chi 2$ (α=0.05, df=1) method. Association between a disease and genotype was established using multiplicative and additive inheritance models. Hypothesis of the reliability of differences between the studied groups was verified using χ^2 Pearson test (for absolute frequencies >10), and Fisher test (for absolute frequencies <5). OR-odds ratio parameters were calculated with 95% confidence interval (95% CI).

Results and Discussion

In evaluation of correspondence of the genotype distribution with Hardy-Weinberg distribution in the studied samples it was

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found that the ratio of the genotype frequencies for all loci of all the studied genes corresponded to this equilibrium. Mutant alleles of the studied polymorphic sites of genes of the plasmic, vasculo-platelet and/or fibrinolytic components of hemostatic system in different combinations were identified in the absolute majority of the studied patients (210 of 213, 98.6%). 'Risk alleles' were completely absent only in three patients (1.4%).

The frequency of carriage of polymorphic variant of F2 (of F7 (G10976A) – 13.4%, of F13 (G226A) – 28.2%, FGB G(-455)A – 24.9%, ITGA2-α2 (C807T) – 41.5%, of ITGB3-b (T1565C) – 15.5%, of PAI-1 4G(-675)5G – 56.6%. Homozygous genotypes for 'risk alleles' in F2 и F5 were not found, in F7 gene they were found in 1.4% of patients, in F13 gene – in 7.5% of patients, in FGB gene – in 4.7%, in ITGA2 gene – in 14.1%, in ITGB3 gene – in 2.3%, in PAI-1 gene – in 32.4% (Table 1).

In comparison of the incidence of 'risk alleles' with the data presented in dbSNP (Table 2), there was found a statistically significant exceedance of the incidence of A allele in F5 gene (p=0.0169), of A allele in FGB gene (p<0.0001) and of T allele in ITGA2 gene (p=0.0201 in the studied group. For other 'risk alleles' no statistically significant difference in the incidence was found as compared to the world population [17].

Table 1

Distribution of Frequencies of Genotypes and Alleles of Genes of Blood Coagulation Factors in Oncological Patients depending on Gender

Gene	Genotype/ Allele	Men, n=70		Women, n=143		Total (main group), n=213	
		abs.	%	abs.	%	abs.	%
F2	20210 GG	67	95.7	139	97.2	206	96.7
	20210 GA	3	4.3	4	2.8	7	3.3
	20210 AA	0	0.0	0	0.0	0	0.0
	G	137	97.9	282	98.6	419	98.4
	A	3	2.1	4	1.4	7	1.6
F5	1691 GG	64	91.4	134	93.7	198	93.0
	1691 GA	6	8.6	9	6.3	15	7.0
	1691 AA	0	0.0	0	0.0	0	0.0
	G	134	95.7	277	96.9	411	96.5
	A	6	4.3	9	3.1	15	3.5
F7	10976 GG	50	71.4	109	76.2	159	74.6
	10976 GA	20	28.6	31	21.7	51	23.9
	10976 AA	0	0.0	3	2.1	3	1.4
	G	120	85.7	249	87.1	369	86.6
	A	20	14.3	37	12.9	57	13.4
F13	GG	33	47.1	76	53.1	109	51.2
	GT	32	45.7	56	39.2	88	41.3
	TT	5	7.1	11	7.7	16	7.5
	G	98	70.0	208	72.7	306	71.8
	T	42	30.0	78	27.3	120	28.2
FGB	(-455) GG	34	48.6	83	58.0	117	54.9
	(-455) GA	33	47.1	53	37.1	86	40.4
	(-455) AA	3	4.3	7	4.9	10	4.7
	G	101	72.1	219	76.6	320	75.1
	A	39	27.9	67	23.4	106	24.9
ITGA2	CC	26	37.1	40	28.0	66	31.0
	CT	36	51.4	81	56.6	117	54.9
	TT	8	11.4	22	15.4	30	14.1
	C	88	62.9	161	56.3	249	58.5
	T	52	37.1	125	43.7	177	41.5

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ITGB3	1565 TT	48	68.6	104	72.7	152	71.4
	1565 TC	20	28.6	36	25.2	56	26.3
	1565 CC	2	2.9	3	2.1	5	2.3
	T	116	82.9	244	85.3	360	84.5
	C	24	17.1	42	14.7	66	15.5
PAI-1	(-675) 5G5G	14	20.0	27	18.9	41	19.2
	(-675) 5G4G	32	45.7	71	49.7	103	48.4
	(-675) 4G4G	24	34.3	45	31.5	69	32.4
	5G	60	42.9	125	43.7	185	43.4
	4G	80	57.1	161	56.3	241	56.6

Notes: mutant alleles are accentuated semi-bold, for all comparisons p>0.05

In study of the distribution of genotype and allele frequencies depending on the oncological diagnosis we established the following statistically significant regularities (Table 3): polymorphic variant of F5 (G1691A) was more commonly determined in patients with LC (8.3%) as compared to TGIT at p=0.03 (1.4%, $\chi2$=4.85); F7 (G10976A) in heterozygous condition was more common in patients with LC as compared to lymphomas at p=0.03 (6.7%, $\chi2$=4.63); F13 (G226A) in homozygous condition for a mutant allele was more common in patients with lymphomas (20.0%) as compared to BC at p=0.03 (2.7%, $\chi2$=6.94; OR=0.11, 95% CI: 0.02-0.75); FGB G(-455)A in homozygous condition for the mutant allele was more frequent in TGIT (4.3%) as compared to LC (0.0%, p=0.03, $\chi2$=4.49) and TFRO (0.0%, p=0.03, $\chi2$=4.81).

Of the total number of patients of the main group one alternative allele was identified in 14 patients (6.6%), two – in 45 (21.1%), three – in 78 (36.6%), four – in 51 (23.9%), five – in 18 (8.5%), six – in 4 (1.9%). That is, in the absolute amount of patients – 196 (92.0%) combinations of several alternative alleles were found in different polymorphic sites of hemostatic system. The analysis of different variants of gene-gene combinations identified 126 genetic profiles in 213 oncological patients.

Table 2

Distribution of Frequencies of 'Risk Alleles' of Genes of Blood Coagulation Factors in Groups of Study as Compared to dbSNP Data Base of National Center of Biotechnological Information (NCBI) TOPMED

SNP	Frequency in Oncological Patients (data obtained by us)	TOPMED Frequency [17]	p
F2 G20210A	A=0.016 (7/426)	A=0.00995 (1250/125568)	0.1793
F5 G1691A	A=0.035 (15/426)	A=0.01926 (2418/125568)	0.0169
F7 G10976A	A=0.134 (57/426)	A=0.11534 (14483/125568)	0.2338
F13 G226A	A=0.282 (120/426)	A=0.21382 (26849/125568)	0.0007
FGB G(-455)A	A=0.249 (106/426)	A=0.15431 (19376/125568)	<0.0001
ITGA2 C807T	T=0.415 (177/426)	T=0.36129 (45367/125568)	0.0201
ITGB3-b T1565C	C=0.155 (66/426)	C=0.12551 (15760/125568)	0.0674
PAI-1 4G(-675)5G	C=0.566 (241/426)	–	–

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Table 3

Distribution of Frequencies of Genotypes and Alleles of Genes of Hemostatic System in Oncological Patients Depending on Diagnosis

Gene	Geno-type/ Allele	BC, n=73		LC, n=18		TFRS, n=16		TGIT, n=69		Lymphomas, n=15		Others, n=22	
		abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
F2	20210 GG	70	95.9	18	100.0	16	100.0	67	97.1	14	93.3	21	95.5
	20210 GA	3	4.1	0	0.0	0	0.0	2	2.9	1	6.7	1	4.5
	20210 AA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	G	143	97.9	36	100.0	32	100.0	136	98.6	29	96.7	43	97.7
	A	3	2.1	0	0.0	0	0.0	2	1.4	1	3.3	1	2.3
F5	1691 GG	67	91.8	15	83.3[1]	15	93.8	67	97.1[1]	14	93.3	20	90.9
	1691 GA	6	8.2	3	16.7[1]	1	6.3	2	2.9[1]	1	6.7	2	9.1
	1691 AA	0	0.0	0	0.0[1]	0	0.0	0	0.0[1]	0	0.0	0	0.0
	G	140	95.9	33	91.7[1]	31	96.9	136	98.6[1]	29	96.7	42	95.5
	A	6	4.1	3	8.3[1]	1	3.1	2	1.4[1]	2	6.7	2	4.5
F7	10976 GG	55	75.3	11	61.1[2]	12	75.0	51	73.9	14	93.3[2]	16	72.7
	10976 GA	17	23.3	7	38.9[2]	3	18.8	18	26.1	1	6.7[2]	5	22.7
	10976 AA	1	1.4	0	0.0[2]	1	6.3	0	0.0	0	0.0[2]	1	4.5
	G	127	87.0	29	80.6	27	84.4	120	87.0	29	96.7	37	84.1
	A	19	13.0	7	19.4	5	15.6	18	13.0	1	3.3	7	15.9
F13	GG	43	58.9[3]	9	50.0	9	56.3	31	44.9	7	46.7[3]	10	45.5
	GT	28	38.4[3]	7	38.9	5	31.3	32	46.4	5	33.3[3]	11	50.,0
	TT	2	2.7[3]	2	11.1	2	12.5	6	8.7	3	20.0[3]	1	4.5
	G	114	78.1	25	69.4	23	71.9	94	68.1	19	63.3	31	70.5
	T	32	21.9	11	30.6	9	28.1	44	31.9	11	36.7	13	29.5
FGB	(-455) GG	44	60.3	13	72.2[5.7]	12	75.0[4.6]	31	44.9[4.5]	7	46.7	10	45.5[6.7]
	(-455) GA	26	35.6	5	27.8[5.7]	4	25.0[4.6]	35	50.7[4.5]	8	53.3	8	36.4[6.7]
	(-455) AA	3	4.1	0	0.0[5.7]	0	0.0[4.6]	3	4.3[4.5]	0	0.0	4	18.2[6.7]
	G	114	78.1	31	86.1[7]	28	87.5[6]	97	70.3	22	73.3	28	63.6[6.7]
	A	32	21.9	5	13,9[7]	4	12.5[6]	41	29.7	8	26.7	16	36.4[6.7]
ITGA2	CC	23	31.5	6	33.3	4	25.0	25	36.2	3	20.0	5	22.7
	CT	39	53.4	9	50.0	9	56.3	36	52.2	11	73.3	13	59.1
	TT	11	15.1	3	16.7	3	18.8	8	11.6	1	6.7	4	18.2
	C	85	58.2	21	58.3	17	53.1	86	62.3	17	56.7	23	52.3
	T	61	41.8	15	41.7	15	46.9	52	37.7	13	43.3	21	47.7
ITGB3	1565 TT	48	65.8	14	77.8	13	81.3	48	69.6	12	80.0	17	77.3
	1565 TC	24	32.9	4	22.2	2	12.5	18	26.1	3	20.0	5	22.7
	1565 CC	1	1.4	0	0.0	1	6.3	3	4.3	0	0.0	0	0.0
	T	120	82.2	32	88.9	28	87.5	114	82.6	27	90.0	39	88.6
	C	26	17.8	4	11.1	4	12.5	24	17.4	3	10.0	5	11.4
PAI-1	(-675)5G5G	14	19.2	4	22.2	3	18.8	11	15.9	3	20.0	6	27.3
	(-675)5G4G	37	50.7	9	50.0	6	37.5	40	58.0	4	26.7	7	31.8
	(-675)4G4G	22	30.1	5	27.8	7	43.8	18	26.1	8	53.3	9	40.9
	5G	65	44.5	17	47.2	12	37.5	62	44.9	10	33.3	19	43.2
	4G	81	55.5	19	52.8	20	62.5	76	55.1	20	66.7	25	56.8

Notes: statistically significant differences at $p<0.05$ between groups: [1] – LC and TGIT ($p=0.03$, $\chi2=4.85$); [2] – LC and lymphomas ($p=0.03$, $\chi2=4.63$); [3] – BC and lymphomas ($p=0.03$, $\chi2=6.94$); [4] – TFRS and TGIT ($p=0.03$, $\chi2=4.81$); [5] – LC and TGIT ($p=0.03$, $\chi2=4.49$); [6] – TFRS and others ($p=0.02$, $\chi2=5.44$; for A allele OR=0.25, 95% CI: 0.07-0.84); [7] – LC and others ($p=0.02$, $\chi2=5.17$; for A allele OR=0.28, 95% CI: 0.09-0.87)

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Table 4

Most Frequent Genetic Profiles of Hemostatic System in Oncological Patients

Genes/Polymorphism	F2: 20210 G>A	F5: 1691 G>A	F7: 10976 G>A	F13: G>T	FGB: -455 G>A	ITGA2: 807 C>T	ITGB3: 1565 T>C	PAI-1: -675 5G>4G	Number of Patients with the Given Profile
Genetic Profile	GG	GG	GG	GT	GG	CT	TT	4G4G	8
	GG	GG	GG	GT	GG	CT	TT	5G4G	6
	GG	GG	GG	GT	GA	CC	TT	4G4G	5
	GG	GG	GG	GG	GG	CT	TT	4G4G	5
	GG	GG	GG	GG	GG	TT	TT	4G4G	5
	GG	GG	GG	GG	GG	CT	TC	5G4G	5
	GG	GG	GG	GG	GA	CT	TT	4G4G	4
	GG	GG	GG	GT	GA	CT	TT	5G4G	4
	GG	GG	GG	GG	GG	CT	TT	5G4G	4
	GG	GG	GG	GG	GG	CT	TT	5G5G	4

Note: mutant alleles are accentuated semi-bold

Most of them (81) were unique and occurred only once, 15 profiles repeated in two patients, 16 in three ones. Ten genetic profiles occurring more often than others are presented in Table 4. However, even among frequently occurring genetic profiles no predomination of any one was found characteristic of a specific nosological form.

In view of the variety of gene-gene combinations it seemed interesting to us to analyze distribution of frequencies of the identified variants in components of hemostatic system (Table 5). Alternative alleles only in genes of plasmic component of hemostasis were found in eight patients (3.8%), including four genes (1.9%) possessing procoagulant ((F2 (G20210A), F5 (G1691A), FGB G(-455)A)), three genes (1.4%) possessing anticoagulant potential ((F7 (G10976A), F13 (G226A)) and one gene (0.5%) possessing opposite action (pro- and anticoagulant).

Alternative alleles in genes of only vasculo-platelet component ((ITGA2-α2 (C807T) and ITGB3-b (T1565C)) were found in seven patients (3.3%), only of fibrinolytic component ((PAI-1 4G(-675)5G)) – in five patients (2.3%). That is, alternative alleles were rarely encountered only in one component of hemostatic system. In 108 patients (50.7% of the total number of patients) alternative alleles were identified in different combinations in genes simultaneously involved in all components of hemostatic system (plasmic, platelet, fibrinolytic), and in 82 patients (38.5%) in genes involved in two components (Table 5).

Despite antithrombotic prophylaxis conducted according to recommendations of RUSSCO, 18 patients (8.5%) in the course of antineoplastic treatment, developed complications in the form of DVT – 13 (6.1%), TEPA – 2 (0.9%), acute cerebrovascular events – 2 (0.9%), myocardial infarction – 1 (0.47%). The genetic profile of the patients with thrombotic complications was also very diverse: not a single repeated profile was found. In F2 (G20210A) polymorphic locus only reference alleles were found, in F5 (G1691A) locus alternative allele was identified in three patients (16.7% of patients with VTEC), F7 (G10976A) – in six (33.3%), F13 (G226A –

in nine (50.0%), FGB G(-455)A – in 8 (44.4%), ITGA2-α2 (C807T) – in 14 (77.8%), ITGB3-b (T1565C) – in 2 (11.11%), PAI-1 4G(-675)5 – in 14 patients (77.8%).

Table 5

Distribution of SNR Detection Frequency in Components of Hemostatic System in Oncological Patients

№ п/п	Variants of SNR Combinations Determined in Components of Hemostatic System	n=213	
		abs	%
1	No SNP	3	1.4
2	SNP in genes of plasmic component (procoagulant)	4	1.9
3	SNP in genes of plasmic component (anticoagulant)	3	1.4
4	SNP in genes of plasmic component (pro- and anticoagulant)	1	0.5
5	SNP in genes of plasmic (pro- and anticoagulant) and platelet components	9	4.2
6	SNP in genes of plasmic (pro- and anticoagulant) and fibrinolytic components	17	8.0
7	SNP in genes of plasmic (pro- and anticoagulant), platelet and fibrinolytic components	41	19.2
8	SNP in genes of plasmic (procoagulant), and platelet components	3	1.4
9	SNR in genes of plasmic (procoagulant) and fibrinolytic components	4	1.9
10	SNP in genes of plasmic (procoagulant), platelet and fibrinolytic components	29	13.6
11	SNP in genes of plasmic (anticoagulant) and platelet components	10	4.7
12	SNR in genes of plasmic (anticoagulant) and fibrinolytic components	12	5.6
13	SNP in genes of plasmic (anticoagulant), platelet and fibrinolytic components	38	17.8
14	SNP in genes of platelet component	7	3.3
15	SNP in genes of fibrinolytic component	5	2.3
16	SNP in genes of platelet and fibrinolytic components	27	12.7

The analysis of frequency of 'risk alleles' in genes of hemostatic system in oncological patients with and without thrombotic complications developed in the course of antineoplastic treatment, no statistically significant differences were found (Table 6).

Table 6

Frequency of Minor Alleles in Genes of Hemostatic System in Oncological Patients with and without Thrombotic Complications

SNP	Frequency in Patients with Thrombotic Complications	Frequency in Patients without Thrombotic Complications	p
F2 G20210A	A=0.0 (0/36)	A=0.017 (7/390)	0.4176
F5 G1691A	A=0.083 (3/36)	A=0.031 (12/390)	0.1245
F7 G10976A	A=0.167 (6/36)	A=0.131 (51/390)	0.3465
F13 G226A	A=0.306 (11/36)	A=0.279 (109/390)	0.4356
FGB G(-455)A	A=0.250 (9/36)	A=0.249 (97/390)	0.5621
ITGA2 C807T	T=0.444 (16/36)	T=0.413 (161/390)	0.4210
ITGB3-b T1565C	C=0.056 (2/36)	C=0.164 (64/390)	0.0591
PAI-1 4G(-675)5G	C=0.472 (17/36)	C=0.574 (224/390)	0.1569

Proceeding to discussion of the obtained results, it is first of all necessary to note that attempts to stratify the risk of appearance of VTEC in patients with cancer were undertaken in several studies. J.W. Blom, et al. showed in their work that patients with hematological malignant neoplasms with correction to age were under the highest risk of venous thrombosis, followed by patients with cancer of lungs and of GIT [15]. According to F. Horsted, et al., the highest risk for VTEC was associated with tumors of the brain and pan-

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creatic cancer [9], and to the estimates of M. Li, et al. – with tumors of bones, soft tissues (10.6%) and with LC (8.1%) [10]. According to the data of our clinics, the highest risk for thrombotic complications was associated with malignant tumors of the GIT and with cervical cancer [18]. No gender differences were found by us in distribution of the frequency of genotype and alleles of blood coagulation factors in oncological patients which differs from the studies conducted in Barnaul where it was found that the frequency of carriage of mutant A allele in F2 (G20210A) polymorphic locus was statistically significantly higher in girls, and of 4G allele in PAI-1 4G(-675)5 locus – in boys [19].

In our study a statistically significant increase in frequency of 'risk alleles' in the group of oncological patients was found in polymorphic sites F5 G1691A (A=0.035, p=0.0169), F13 G226A (A=0.282, p=0.0007), FGB G(-455)A (A=0.249, p<0.0001) and ITGA2-α2 C807T (T=0.415, p=0.0201). As compared to the world population. The presence of hereditary thrombophilia in a patient does not suggest basal chronic hypercoagulation, but determines the exaggerated response of the hemostatic system to traditional provoking influences in the form of excessively high or prolonged regeneration of active thrombin which may lead to faster initiation and spread of thrombotic process [20]. Such provoking actions in oncological patients include both surgical support, chemo- and radiological treatment, and the disease itself. We did not find any statistically significant differences in the incidence of 'risk alleles' in genes of hemostatic system in patients with thrombotic complications developed in the course of antineoplastic therapy, and in those without them. It can be suggested that the rate of development of VTEC is to a larger extent determined by the character of the neoplastic process and by the conducted chemotherapy, and not by genetic factors. At the same time, in our study, in comparison of frequencies of genotypes and alleles between the groups only isolated SNR were analyzed. Taking into account the facts of recording of combinations of several 'risk alleles' in different polymorphic sites of genes of hemostatic system in 92.0% of patients, the variety of gene-gene combinations in the studied sample, and also the data of potentiation of the thrombogenic effect in case of carriage of several procoagulant mutations [21], we consider it necessary to study the influence of combined SNR on development of thrombotic complications in oncological patients in the large sample.

A high frequency of 'risk alleles' not only in plasmic, but also in vasculo-platelet component of hemostatic system shows the necessity to add antiaggregants to prophylactic anticoagulant therapy in the period of treatment of the main disease (chemoradiotherapy, postoperative period), if there are no contraindications to their administration. However, this point also requires additional investigations.

Conclusion

The results of study demonstrated statistically significant exceedance of the frequency of 'risk alleles' of polymorphic loci F5 G1691A (A=0.035, p=0.0169), F13 G226A (A=0.282, p=0.0007), FGB G(-455)A (A=0.249, p<0.0001) and ITGA2-α2 C807T (T=0.415, p=0.0201) in the group of oncological patients as compared to the world population. In the same polymorphic loci except ITGA2-α2 (C807T), statistically significant differences in the frequency of alternative alleles in different localizations of an oncological process were found. In 92.0% of patients a combination of SNR in different components of hemostatic system was determined that requiresunderlying studying reasonability of use of antiaggregant therapy along with anticoagulant therapy.

Литература

1. Rosendaal F.R., Reitsma P.H. Genetics of venous thrombosis // Journal of Thrombosis and Haemostasis. 2009. Suppl. 1. P. 301-304. doi:10.1111/

j.1538-7836.2009.03394.x
2. Naess I.A., Christiansen S.C., Romundstad P., et al. Incidence and mortality of venous thrombosis: a population-based study // Journal of Thrombosis and Haemostasis. 2007. Vol. 5, №4. P. 692-699. doi:10.1111/j.1538-7836.2007.02450.x
3. Kyrle P.A., Minar E., Bialonczyk C., et al. The risk of recurrent venous thromboembolism in men and women // The New England Journal of Medicine. 2004. Vol. 350, №25. P. 2558-2563. doi:10.1056/NEJMoa032959
4. Воробьев А.В., Макацария А.Д., Чабров А.М., и др. Синдром Труссо: современный взгляд на проблему // Журнал акушерства и женских болезней. 2015. Т. 64, №4. С. 85-94.
5. Falanga A., Marchetti M. Hemostatic biomarkers in cancer progression // Thrombosis Research. 2018. Vol. 164, Suppl 1. P. S54-S61. doi:10.1016/j.thromres.2018.01.017
6. Cronin-Fenton D.P., Sondergaard F., Pedersen L.A., et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006 // British Journal of Cancer. 2010. Vol. 103, №7. P. 947-953. doi:10.1038/sj.bjc.6605883
7. Chew H.K., Wun T., Harvey D., et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers // Archives of Internal Medicine. 2006. Vol. 166, №4. P. 458-464. doi:10.1001/archinte.166.4.458
8. Francis C.W., Kessler C.M., Goldhaber S.Z., et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study // Journal of Thrombosis and Haemostasis. 2015. Vol. 13, №6. P. 1028-1035. doi:10.1111/jth.12923
9. Horsted F., West J., Grainge M.J. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis // PLoS Medicine. 2012. Vol. 9, №7. P. e1001275. doi:10.1371/journal.pmed.1001275
10. Li M., Guo Q., Hu W. Incidence, risk factors, and outcomes of venous thromboembolism after oncologic surgery: A systematic review and meta-analysis // Thrombosis Research. 2019. Vol. 173. P. 48-56. doi:10.1016/j.thromres.2018.11.012
11. Lee A.Y., Peterson E.A. Treatment of cancer-associated thrombosis // Blood. 2013. Vol. 122, №14. P. 2310-2317. doi:10.1182/blood-2013-04-460162
12. Timp J.F., Braekkan S.K., Versteeg H.H., et al. Epidemiology of cancer-associated venous thrombosis // Blood. 2013. Vol. 122, №10. P. 1712-1723. doi:10.1182/blood-2013-04-460121
13. Vossen C.Y., Hoffmeister M., Chang-Claude J.C., et al. Clotting factor gene polymorphisms and colorectal cancer risk // Journal of Clinical Oncology. 2011. Vol. 29, №13. P. 1722-1727. doi:10.1200/JCO.2010.31.8873
14. Tinholt M., Viken M.K., Dahm, A.E., et al. Increased coagulation activity and genetic polymorphisms in the F5, F10 and EPCR genes are associated with breast cancer: a case-control study // BMC Cancer. 2014. Vol. 14. P. 845. doi:10.1186/1471-2407-14-845
15. Blom J.W., Doggen C.J., Osanto S., et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis // JAMA. 2005. Vol. 293, №6. P. 715-722. doi:10.1001/jama.293.6.715
16. Воробьев А.В., Чабров А.М., Савченко А.А., и др. Вопросы патогенеза синдрома Труссо // Акушерство, гинекология и репродукция. 2015. Т. 9, №2. С. 99-109. doi:10.17749/2070-4968.2015.9.2.099-109
17. Smigielski E.M., Sirotkin K., Ward M., et al. dbSNP: a database of single nucleotide polymorphisms // Nucleic Acids Research. 2000. Vol. 28, №1. P. 352-355. doi:10.1093/nar/28.1.352
18. Кит О.И., Кательницкая О.В., Гуськова Н.К., и др. Опыт лечения венозных тромбоэмболических осложнений в онкологии дабигатраном // Флебология. 2016. Т. 10, №1. С. 29-34. doi:10.17116/flebo201610129-34
19. Строзенко Л.А., Гордеев В.В., Лобанов Ю.Ф., и др. Частота носительства полиморфных вариантов генов факторов свертывания крови у подростков города Барнаул // Сибирское медицинское обозрение. 2015. №3. С. 53-56.
20. Лобастов К.В., Баринов В.Е., Счастливцев И.В., и др. Современные подходы к диагностике и терапии острого венозного тромбоза. М.: Триумф; 2016.
21. Пизова Н.В. Тромбофилии: генетические полиморфизмы и сосудистые катастрофы. М.: ИМА-ПРЕСС; 2013.

References

1. Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. *Journal of Thrombosis and Haemostasis.* 2009;Suppl. 1:301-4. doi:10.1111/j.1538-7836.2009.03394.x
2. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. *Journal of Thrombosis and Haemostasis.* 2007;5(4):692-9. doi:10.1111/j.1538-7836.2007.02450.x
3. Kyrle PA, Minar E, Bialonczyk C, et al. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med*. 2004;350(25):2558-63. doi:10.1056/NEJMoa032959
4. Vorobev AV, Makatsaria AD, Chabrov AM, et al. Pathogenesis of Trousseau's syndrome. *Journal of Obstetrics and Woman's Diseases*. 2015;64(4):85-94. (In Russ).
5. Falanga A, Marchetti M. Hemostatic biomarkers in cancer progression. *Thrombosis Research*. 2018;164

DOI:10.23888/PAVLOVJ202028144-56

(Suppl 1):S54-S61. doi:10.1016/j.thromres.2018.01.017
6. Cronin-Fenton DP, Sondergaard F, Pedersen LA, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *British Journal of Cancer*. 2010;103(7):947-53. doi:10.1038/sj.bjc.6605883
7. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Archives of Internal Medicine.* 2006;166(4):458-64. doi:10.1001/archinte.166.4.458
8. Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study. *Journal of Thrombosis and Haemostasis.* 2015;13(6):1028-35. doi:10.1111/jth.12923
9. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Medicine.* 2012;9(7):e1001275. doi:10.1371/journal.pmed.1001275
10. Li M, Guo Q, Hu W. Incidence, risk factors, and outcomes of venous thromboembolism after oncologic surgery: A systematic review and meta-analysis. *Thrombosis Research*. 2019;173:48-56. doi:10.1016/j.thromres.2018.11.012
11. Lee AY, Peterson EA. Treatment of cancer-associated thrombosis. *Blood*. 2013;122(14):2310-7. doi:10.1182/blood-2013-04-460162
12. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122(10):1712-23. doi:10.1182/blood-2013-04-460121
13. Vossen CY, Hoffmeister M, Chang-Claude JC, et al. Clotting factor gene polymorphisms and colorectal cancer risk. *Journal of Clinical Oncology*. 2011;29(13):1722-7. doi:10.1200/JCO.2010.31.8873
14. Tinholt M, Viken MK, Dahm AE, et al. Increased coagulation activity and genetic polymorphisms in the F5, F10 and EPCR genes are associated with breast cancer: a case-control study. *BMC Cancer*. 2014;14:845. doi:10.1186/1471-2407-14-845
15. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-22. doi:10.1001/jama.293.6.715
16. Vorobev AV, Chabrov AM, Savchenko AA., et al. Pathogenesis of Trousseau's syndrome. *Obstetrics, Gynecology and Reproduction*. 2015;9(2):99-109. (In Russ). doi:10.17749/2070-4968.2015.9.2.099-109
17. Smigielski EM, Sirotkin K, Ward M, et al. dbSNP: a database of single nucleotide polymorphisms. *Nucleic Acids Research*. 2000;28(1):352-5. doi:10.1093/nar/28.1.352
18. Kit OI, Katelnitskaya OV, Guskova NK, et al. Experience with the treatment of venous thromboembolism in oncology patients with the use of dabigatran. *Flebologiya*. 2016;10(1):29-34. (In Russ). doi:10.17116/flebo201610129-34
19. Strozenko LA, Gordeev VV, Lobanov YF, et al. Frequency of carriage of the polymorphic gene variants of clotting factors in adolescents in Barnaul. *Siberian Medical Review*. 2015;(3):53-6. (In Russ).
20. Lobastov KV, Barinov VE, Schastlivtsev IV, et al. *Sovremennye podkhody k diagnostike i terapii ostrogo venoznogo tromboza*. Moscow: Triumf; 2016. (In Russ).
21. Pizova NV. *Trombofilii: geneticheskie polimorfizmy i sosudistye katastrofy*. Moscow: IMA-PRESS; 2013. (In Russ).

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