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Chapter 16

Ethnic Differences in Susceptibility to the Effects of Platinum-Based Chemotherapy

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Abstract

There is substantial interindividual variability in the efficacy and tolerability of anticancer drugs. Such differences can be greater between individuals of different ethnicities. The clinical studies demonstrate that individuals from Asia (East Asia) are more susceptible to the effects of platinum-containing chemotherapies than their Western counterparts. To determine whether population-related genomics (i.e., frequencies of DNA polymorphisms) contribute to differences in patient outcomes, polymorphisms in 109 genes involved mainly in xenobiotic metabolism, DNA repair, the cell cycle, and apoptosis were tested in Russian (Caucasians) and Yakut (North Asians) ovarian cancer patients receiving cisplatin-based chemotherapy. Totally, 232 polymorphisms were genotyped in individual DNA samples using conventional PCR and arrayed primer extension technology. Single nucleotide polymorphisms (SNPs) in more than 30 genes were found to be associated with one or more of clinical end points (i.e., tumor response, progression-free survival, overall survival, and side effects). However, all associations between SNPs and clinical outcomes were specific for each of ethnic group studied. These findings let us to propose the existence of distinctive ethnic-related characteristics in molecular mechanisms determining the sensitivity of patients to platinum drug effects.

Keywords: cisplatin, DNA polymorphisms, ethnic diversity, chemotherapy, ovarian cancer

1. Introduction

There is substantial interindividual variability in the efficacy and tolerability of pharmaceuticals, including anticancer drugs. Such differences can be greater between individuals of different

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ethnicities [1]. Currently, pharmacoethnicity, or ethnic diversity in drug effectiveness and/or toxicity, is an increasingly recognized factor for accounting interindividual variations in drug response [2]. Although the reasons underlying ethnic diversity in drug response are likely multifactorial [3], the results of numerous population studies suggest that they may be attributed, at least in part, to the interpopulation differences in frequencies of DNA polymorphisms – inherited variations at the DNA sequence level [4–6]. In terms of F_{ST}, the most commonly used measure of population differentiation; the proportion of such differences is 5–13% of total genetic diversity depending on the type of polymorphic markers chosen [6]. The opponents of ethnic-/race-based explorations in pharmacogenomics often consider these portions of variation as non-essential in the context of considerably larger proportions of within population variation which represents the average difference between members of the same population and accounts for 87–95% of total variance [7, 8]. Nevertheless, significant differences in the population prevalence of functionally impaired allelic variants of genes may create a potential for ethnic differences in responses to drugs that are detoxified (transported or targeted) by the proteins that are encoded by those genes [9–11]. A prominent example how population-based genetic differences can affect the drug response is the significantly greater risk for Stevens-Johnson syndrome and toxic epidermal necrolysis among East/Southeast Asian carbamazepine users, particularly Han-Chinese, Thais, and Malaysians, that has been associated with *HLA-B*1502* allele [12]. The relationship was not evident in non-Asian patients as well as in Japanese and Koreans due to infrequency of the allele in these populations. Another example is the lower average warfarin requirements of Asians linked to the higher frequency of AA genotype at SNP rs9923231 upstream of *VKORC1* gene among them [13]. Finally, considering potential pharmacoethnicity of anticancer drugs, one of the most illustrative examples, although not associated with germline variations, is the higher response rate to EGFR inhibitors (e.g., gefitinib) of Asian (East Asian) lung cancer patients compared to Caucasians that correlates to higher frequencies of activating *EGFR* mutations in East Asians [14].

Keeping all that in mind, we carried out a comparative study aimed to explore the genetic bases of differences between Asian and Caucasian cancer patients in their sensitivity to the effects of platinum-containing chemotherapy. Platinum-based drugs are among the most widely used cytotoxic agents for the treatment of many types of cancer [15]. The first information about lesser tolerance of Asian patients to standard, approved for Europeans, doses of platinum-containing regimens came from Japanese physicians [16]. In both individual small studies and some common arm trials conducted in Japan and by Southwest Oncology Group, the higher frequency of toxicity, particularly hematologic toxicity, was registered in Asian patients than non-Asians (mostly Caucasians) [1, 17]. Moreover, it was also found that the incidence of toxicity was still higher among Asians even after appropriate dose reduction [1]. Although some comparative pharmacogenetic studies have been conducted, the reasons underlying the higher sensitivity/toxicity of Asians to the systemic platinum-containing therapy are not yet well understood [18–20]. To assess the effect of population genomics on difference in patient response, we comparatively explored the results of cisplatin-based chemotherapy in Russian (Caucasians) and Yakut (North Asians) ovarian cancer patients. Principal component analysis, performed by us using genotype data of a common set of 125,000 genome-wide SNPs, demonstrated significant differences between gene pools of Asian and non-Asian populations (**Figure 1**).

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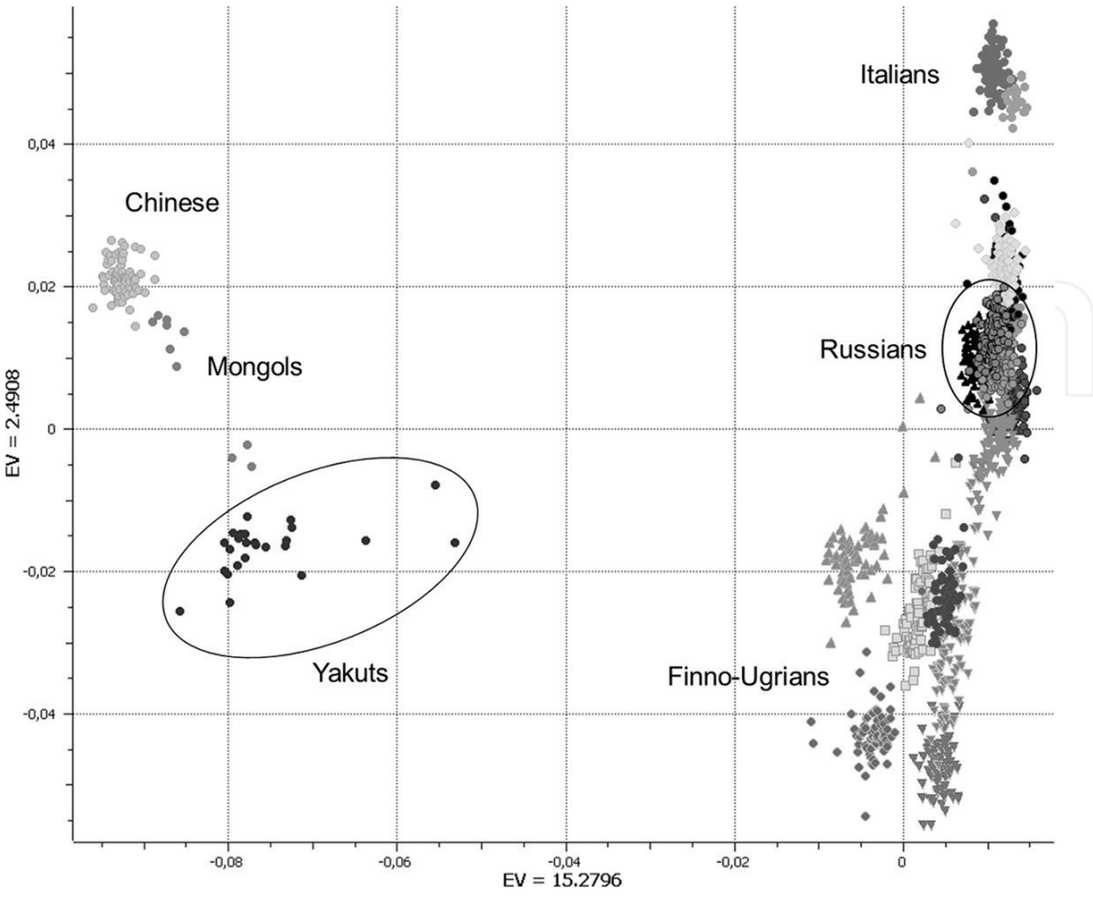


Figure 1. Genetic structure of Eurasian populations (based on 125,000 autosomal SNPs). The first two PCs are shown. Each individual is represented by a sign and the label corresponding to their self-identified population origin.

The estimates, obtained using the same set of polymorphic markers, showed that a portion of variation accounted for population-related differences, F_{ST}, in allele frequency between Russians and Yakuts was as high as 0.08, creating the potential for searching a causative polymorphism(s) with corresponding prevalence in population frequency. In the current study such candidates were searched among 232 polymorphisms from 109 genes involved mainly in xenobiotic metabolism, DNA repair, the cell cycle, and apoptosis.

2. Materials and methods

2.1. Patients

Ovarian cancer patients were identified and treated between 2003 and 2007 years at the N. N. Blokhin Cancer Research Centre and the Yakutsk Republic Cancer Clinic. Once identified, patients were invited to participate and were enrolled after they signed an informed consent. Detailed procedures of patient enrolment and data collection have been described previously [21, 22]. Briefly, unrelated Russian and Yakut women with morphologically confirmed epithelial ovarian carcinoma, who had received no previous chemotherapy or radiation therapy, were recruited. The upper age limit was 65 years. Exclusion criteria were serious concomitant

diseases (diabetes, uncontrolled hypertension, myocardial infarction within the last 6 months, etc.), and clinically significant hearing impairment (grade 2 or higher). To ascertain ethnicity, women completed a questionnaire about their ancestry; only self-described Russian and Yakut patients with no history of interethnic marriages in the past two generations were recruited. Before the initiation of chemotherapy, venous blood samples were obtained for genetic testing. The chemotherapy regimen was intravenous cisplatin (100 mg/m^2) plus cyclophosphamide (600 mg/m^2) on day 1, every 3 weeks, for a maximum of 6 cycles. Intraperitoneal chemotherapy and radiotherapy were not allowed. Toxicity of the treatment was described according to standard National Cancer Institute Common Toxicity Criteria version 2.0 [23]. All patients were assessed for the maximal grades of nephrotoxicity, ototoxicity, neurotoxicity, emesis, neutropenia, anemia, and thrombocytopenia.

The tumor response was assessed every 2 cycles. After the completion of chemotherapy, the patients were followed-up for disease relapse and survival. Patients with progressive disease were treated with second-line chemotherapy, mostly taxane based. The study protocol and informed consent form were approved by the Ethics Committee of the N. N. Blokhin Cancer Research Centre.

2.2. Genotyping

DNA was isolated from the venous blood samples (leukocytes) using a conventional approach including proteinase K treatment with subsequent phenol-chloroform extraction [24]. Some polymorphisms (**Table 1**) were genotyped using a polymerase chain reaction restriction fragment length polymorphism (RFLP)-based technique or determined directly through evaluation of their PCR product lengths.

Other polymorphisms were genotyped using a microarray "DNA repair single nucleotide polymorphism detection test" (version 2, Asper Biotech, Tartu, Estonia). The microarray genotypes 228 SNPs in 106 genes involved in[1] DNA repair, cell cycle control, apoptosis, and xenobiotic metabolism. Most of manually genotyped loci were also in the list of the microarray's polymorphisms and served as controls of genotyping efficiency. To check into account the potential mistakes in genotyping with the microarray [25], all polymorphisms, which were associated with any clinical endpoints, were additionally tested using the RFLP method.

2.3. Statistical analysis

A permutation exact test, a two-sided Fisher exact test, and a χ^2 test were used to determine the relationship between the variables and alleles/genotypes tested. Correlations between survival and genotype or genetic polymorphism were assessed using the Kaplan-Meier product limit method and the log-rank test. The significance of associations was set at $P < 0.05$ [26]. The statistical analyses were performed using the Statistica software (version 6.0, StatSoft, Inc., Tulsa, OK, USA) or the IBM SPSS Statistics software package (version 19, SPSS, Inc., IBM Company, IBM Corporation, Armonk, NY, USA), GraphPadInStat (version 3.00, GraphPad Software, San Diego, CA, USA), and the PowerMarker software (version 3.0) [27].

[1]Alternative variant – "genes which are involved in".

Polymorphism	#rs ID	Genotypes (No. patients)*			P
GSTA1 − 69 C/T	rs3957357	CC (43/60)	CT (49/22)	TT (12/5)	0.0007
GSTM1 gene deletion		0/0 (47/28)	+/0** (57/59)	NA	0.0754
GSTM3 AGG deletion	rs1799735	AGG/AGG (83/75)	AGG/− (16/12)	−/− (5/0)	0.1054
GSTM3 $Val^{224}Ile$	rs7483	Val/Val (39/30)	Val/Ile (57/37)	Ile/Ile (8/20)	<0.0001
GSTP1 $Ile^{105}Val$	rs1695	Ile/Ile (41/67)	Ile/Val (53/17)	Val/Val (10/3)	<0.0001
GSTP1 $Ala^{114}Val$	rs1138272	Ala/Ala (80/84)	Ala/Val (24/3)	—***	0.0001
GSTT1 gene deletion		0/0 (18/22)	+/0** (86/65)	NA	0.2123
ERCC1 19007 T/C	rs11615	TT (43/53)	TC (46/29)	CC (15/5)	0.0146
ERCC1 8092 C/A	rs3212986	CC (61/52)	CA (37/31)	AA (6/4)	0.9351
ERCC2 $Asp^{312}Asn$	rs1799793	Asp/Asp (34/66)	Asp/Asn (50/19)	Asn/Asn (20/2)	<0.0001
ERCC2 $Lys^{751}Gln$	rs13181	Lys/Lys (28/67)	Lys/Gln (54/18)	Gln/Gln (22/2)	<0.0001
XRCC1 $Arg^{194}Trp$	rs1799782	Arg/Arg (94/69)	Arg/Trp (10/18)	—	0.0398
XRCC1 $Arg^{280}His$	rs25489	Arg/Arg (95/80)	Arg/His (9/6)	His/His (0/1)	0.5007
XRCC1 $Arg^{399}Gln$	rs25487	Arg/Arg (49/40)	Arg/Gln (45/39)	Gln/Gln (10/8)	0.9752
TP53 $Arg^{72}Pro$	rs1042522	Arg/Arg (52/47)	Arg/Pro (40/35)	Pro/Pro (12/5)	0.3733
CYP2E1 96bp insertion		−/− (100/74)	−/ins (4/13)	—	0.0097
CYP2E1 − 1053 C/T	rs2031920	CC (102/68)	CT (2/18)	—	<0.0001
CYP2E1 7632 T/A	rs6413432	TT (91/67)	TA (12/20)	AA (1/0)	0.0753
CYP2E1 9896 C/G	rs2070676	CC (82/78)	CG (20/9)	GG (2/0)	0.0908

*The first value in parentheses means the number of patients with corresponding genotype in Russian group, the second one – in Yakut group.

**The genotype was defined as positive if at least one copy of gene was present.

***The corresponding genotype was not occurred in populations.

NA – not available (not determined with the genotyping method used).

Table 1. Genotype frequencies in Russian and Yakut patients.

3. Results and discussion

During 2003–2007 years, 104 Russian patients and 87 Yakut patients were enrolled in the study. The median age of patients was 52 and 51 years, respectively. The majority of patients in both groups had stage III disease (72 and 53 women, respectively). Stages I, II, and IV were detected in 14, 6, and 10 Russian patients and 1, 8, and 25 Yakut patients. A total of 21 Russian patients and 11 Yakut patients were receiving adjuvant chemotherapy and were not eligible for evaluation of tumor response (i.e., they had no residual disease after surgery). Overall response rates, comprising complete and partial responders, were 85% in the Russian group and 58% in the Yakut group.

The median progression-free survival (PFS) in the Russian group was 12 months, and the median overall survival (OS) was 55 months. In the Yakut group, both intervals were shorter —8 and 29 months, respectively. However, being adjusted for disease stage, the values became similar to those for the Russian group.

More contrast results were obtained in analysis of occurrence of adverse events. To assess the association between genotype and the toxicity of the treatment used, patients were classified as having good or poor tolerance to treatment (grades 3–4 of neutropenia, grades 2–4 of anemia, grades 2–4 of neuropathy, grades 3–4 of emesis, all grade of thrombocytopenia, nephrotoxicity, and ototoxicity were considered as clinically significant toxicities). Comparison of the frequencies of side effects registered in Russian and Yakut patients confirmed higher toxicity of platinum-based regimens for patients of Asian origin than for Europeans. Particularly, Yakut patients suffered more frequently than Russians from nephrotoxicity and severe emesis ($P = 0.027$ and $P = 0.061$, respectively), which both were known to be the most common adverse events observed in regimens using cisplatin [28].

Genetic testing of the patients from our groups was performed in two stages. At first, we explored the associations between outcomes of a cisplatin-cyclophosphamide regimen in Russian and Yakut ovarian cancer patients and some most common polymorphisms in several genes [21, 22], among the tested genes, were glutathione S-transferase (GST) genes (*GSTA1, GSTM1, GSTM3, GSTP1* and *GSTT1*), DNA repair genes (*ERCC1, ERCC2* and *XRCC1*) as well as *TP53* and *CYP2E1* genes (**Table 1**). GST and DNA repair genes have been described as important for cisplatin metabolism and activity [29, 30]. GSTs can directly limit the amount of reactive cisplatin species available for interaction with DNA, by catalyzing their binding to tripeptide glutathione. The resulting cisplatin-glutathione conjugates can be further easily excreted from the cell by the GS-X pump transporters [31]. DNA repair proteins remove platinum-DNA adducts, the persistence of which underpins the antitumor potential of platinum drugs. In contrast to GST and the DNA repair proteins, TP53 protein does not seem to directly affect cisplatin metabolism or transformation. At the same time, it has a crucial role in mediating cellular responses to DNA damage, initiating programmed cell death when the effective DNA repair is impossible [29, 30, 32]. There is also no evidence that cisplatin is metabolized by CYP2E1. However, CYP2E1 is a significant potential source of catalytic iron and can serve as a site for generating reactive oxygen species in the presence of cisplatin [33]. It has been proposed that this mechanism underlies cisplatin-induced nephrotoxicity and hepatotoxicity [34, 35].

One of the most significant associations found in the first part of the study was the correlation between the survival time intervals and *GSTP1* Ile105Val polymorphism registered in Russian subjects ($P = 0.004$ and $P = 0.016$ for PFS and OS, respectively). Russian ovarian cancer patients with a homozygous Ile/Ile genotype had longer PFS and OS than those ones who carried Ile/Val and Val/Val genotypes. However, the association was not observed in Yakut patients. PFS and OS of Yakut women with Ile/Ile genotype did not differ from the corresponding time intervals of patients with 1 or 2 Val alleles. In the Yakut group, PFS correlated with *CYP2E1* 7632 T/A polymorphism ($P = 0.015$), being longer in patients with a homozygous TT genotype than in patients with the heterozygous TA genotype.

Analysis of genotype distribution in the population groups for toxicities revealed that occurrence of nephrotoxicity and severe emesis in Yakut patients correlated with *GSTT1* and

CYP2E1 genotypes, respectively. Patients with a homozygous *GSTT1* gene deletion (*GSTT1* null) suffered more frequently from nephrotoxicity than carriers of functional *GSTT1* variants (OR = 3.31, 95% CI 1.15–9.54, P = 0.028). Patients who had a 96 bp insertion in the promoter region of the *CYP2E1* were more prone to severe emesis (OR = 4.69, 95% CI 1.31–16.77, P = 0.027). Grade 3 or 4 emesis was also associated with another *CYP2E1* polymorphism—a single nucleotide substitution (9896 C/G) in intron 7. Patients with a heterozygous CG genotype had a higher risk of severe emesis than patients with the homozygous CC genotype (OR = 16.96, 95% CI 2.01–143.16, P = 0.002). In contrast, in Russian patients, *CYP2E1* polymorphisms were not associated with any clinical outcomes and distribution of *GSTT1* genotypes correlated with severity of emesis. The risk of severe emesis was higher in Russian patients with the *GSTT1*-null genotype than in patients with a functional *GSTT1* variant (OR = 4.06, 95% CI 1.40–11.78; P = 0.014). As for the nephrotoxicity in Russian subjects, it was associated with *ERCC1* 19007 T/C or 8092 C/A polymorphisms, and cases of renal dysfunction were more prevalent among patients with the heterozygous genotypes of each locus. Other found genotype-clinical end point associations were also discordant in Russians and Yakuts (**Table 2**).

When genotype distributions in both groups were compared significant differences in population genotype frequencies were noted for 10 of 19 polymorphisms studied but only 5 of them were associated with clinical outcomes (**Tables 1** and **2**).

Evaluation of the direction/strength of the associations showed that they were not correlated with the differences in population frequencies of corresponding genotypes. For example, the absence of correlation between the *GSTP1* Ile105Val polymorphism and survival in Yakut patients was not simply due to the higher prevalence of Ile/Ile genotype among them because carriers of Ile/Ile genotype did not differ in PFS or OS from those who had genotypes with 1 or 2 Val alleles. Similar results were obtained for the *GSTA1*-69 C/T polymorphism. Its CT and TT genotypes were associated with a risk of anemia in Yakuts; yet the greater frequencies of the CT and TT genotypes in Russians did not result in a higher risk of anemia. Similarly, risk genotypes of *ERCC1* 19007 T/C and ERCC2 Asp312Asn polymorphisms (i.e., heterozygous genotypes in Russians) were not rare among Yakut patients but they did not demonstrate correlations with the corresponding side effects (**Tables 1** and **2**). It seems that only in the case of *CYP2E1* 96 bp insertion polymorphism an effect of allele frequency differences could be proposed but due to small number of individuals with the insertion containing genotypes in Russians the suggestion requires verification in a larger sample.

Taken in the context of other data, the obtained results generally supported the role of ethnicity as an additional reason for differences in the outcomes of clinical trials in which the same treatment is used. At the same time, the results of genetic testing suggested that a single genotypic difference was unlikely to account for the observed ethnic variation in toxicity and survival. Moreover, they also suggested that assessing traditionally tested common polymorphisms in GST and DNA repair genes is not enough for relevant description of lesser tolerability of Asians (North/East Asians) to the effects of platinum-containing chemotherapies and further studies involving more polymorphic markers are required.

In the second part of our study, we systematically investigated the associations between patients' outcomes and SNPs in more than 100 genes using the microarray "DNA repair single nucleotide polymorphism detection test" (version 2) [36, 37]. Like similar genotyping panels, the list of genes tested comprised candidate genes involved in key pathways of cellular

Gene name	#rs ID	Clinical outcomes**															
		PFS		OS		Anemia		Neutropenia		Thrombocitopenia		Nephrotoxicity		Ototoxicity		Emesis	
		R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y
GSTA1	rs3957357						+										
GSTM1	gene deletion					+				+							
GSTM3	rs1799735					+				+							
GSTM3	rs7483																
GSTP1	rs1695	+		+													
GSTP1	rs1138272																
GSTT1	gene deletion												+			+	
ERCC1	rs11615											+					
ERCC1	rs3212986											+					
ERCC2	rs1799793									+							
ERCC2	rs13181																
XRCC1	rs1799782																
XRCC1	rs25489																
XRCC1	rs25487							+									
TP53	rs1042522							+									
CYP2E1	96bp insertion																+
CYP2E1	rs2031920																
CYP2E1	rs6413432		+														
CYP2E1	rs2070676																+

*The registered associations are indicated by "+" in the corresponding cells.

**Tumor response and ototoxicity were not included in the table as there were no associations between them and polymorphisms tested.

Table 2. The associations between polymorphisms and clinical outcomes observed in Russian (R) and Yakut (Y) patient groups (the first stage of the study)*.

response to different drugs [38, 39], including many genes that are related to the cisplatin pathway (platinum pathway) [40]. A total of 213 SNPs from 228 genotyped SNPs were new (i.e., they did not include SNPs from the first stage) and 27 SNPs were associated with one or more of the assessed clinical end points (**Table 3**).

Increasing number of polymorphisms yielded an association with tumor response. To assess the association, patients who achieved a complete remission were compared with those without it (i.e., patients with partial response, stable and progressive disease). In the Russian group, a significant difference in complete response was observed according to polymorphism in the *ADH1C* gene (A/G, rs698) (P = 0.0002). The proportion of patients who achieved a complete response was higher among carriers of homozygous genotypes AA and GG compared with patients with a heterozygous variant AG. In Yakut patients, the occurrence of complete response was correlated with an allelic status of SNP in *CDKN1B* gene (T/C, rs34330), particularly with an allele C. There were no cases of complete remission among patients who carried a homozygous genotype TT at rs34330. The SNP was also associated with PFS in Yakut subjects (P = 0.0051); patients with the genotype TT had shorter PFS than patients with CC and CT genotypes. The protein encoded by *CDKN1B* gene participates in regulation of the cell cycle by binding and inhibiting activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus blocking the transition of the cell into the S-phase. C > T substitution at rs34330 locus results in decreasing the levels of mRNA and CDKN1B protein [41]. Reduced level of *CDKN1B* expression has been associated with a poor outcome in various cancers [42, 43]. In contrast, the *ADH1C* SNP (rs698) has been associated with a risk of alcoholism and ethanol-related cancers [44], but our study was the first to demonstrate an association with a chemotherapy outcome (i.e., tumor response) but the mechanism is not obvious.

Genotypes of seven SNPs were associated with differences in PFS in the Russian group (**Table 3**). The most significant SNPs were rs1142345 (A/G) in *TPMT* ($P = 3 \times 10^{-8}$) and rs4986998 (C/T) and rs1800566 (C/T) in *NQO1* genes ($P = 2 \times 10^{-6}$ and $P = 9 \times 10^{-11}$, respectively). The longer PFS was seen in patients with the most frequent genotypes AA and CC. SNPs in *NQO1* demonstrated similar correlations with OS.

Thiopurine S-methyltransferase (TPMT) is a cytosolic methylating enzyme with unknown physiological role [45]. However, this enzyme is known to be able to catalyze the S-methylation of some aromatic and heterocyclic compounds, particularly thio-compounds (e.g., 6-mercaptopurine and 6-thioguanine). Discussing the associations revealed between SNPs in *TPMT* and cisplatin ototoxicity, Ross et al. [46] have hypothesized that TPMT can affect cisplatin-induced hearing impairment through inactivation of cisplatin-purine compounds that form cytotoxic DNA cross-links, and cause cell death. As might be expected from that data, those patients in our study who had the loss-of-function genotype AG at rs1142345 should demonstrate a better outcome as a result of decreased inactivation of cisplatin-purine compounds, but such a correlation was not observed. Moreover, patients with an AG genotype had even shorter PFS than those who carried the functionally normal AA genotype.

The tested SNPs in *NQO1* gene are characteristic polymorphic variants affecting functional ability of the corresponding protein — a cytosolic flavoenzyme NAD(P)H: quinone oxidoreductase 1 (NQO1). *NQO1* polymorphic status has been associated with anticancer chemotherapy

Gene name	#rs ID	Clinical outcomes																	
		Response		PFS		OS		Anemia		Neutropenia		Thrombocitopenia		Nephrotoxicity		Ototoxicity		Emesis	
		R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y
ADH1C	rs698	+																	
ALDH2	rs4646777			+															
APEX1	rs1048945															+			
CCNH	rs2266690							+											
COMT	rs4633			+															
CDKN1B	rs34330		+		+														
CYP1A1	rs4646903						+												
CYP1A2	rs2470890						+												
DRD2	rs1079597			+															
EPHX1	rs1051740							+						+					
EPHX1	rs2234922																+		
ERCC5	rs1047768									+									
ERCC5	rs17655									+									
GRPR	rs4986946			+															
GSTA4	rs405729							+											
LIG3	rs1052536									+									
MSH3	rs26279											+							
MSH6	rs1042821																	+	
MUTYH	rs3219484									+									
MUTYH	rs3219489									+									
NAT2	rs1801280							+											

Gene name	#rs ID	Clinical outcomes																	
		Response		PFS		OS		Anemia		Neutropenia		Thrombocitopenia		Nephrotoxicity		Ototoxicity		Emesis	
		R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y	R	Y
NBN	rs1063045																		+
NQO1	rs1800566			+		+													
NQO1	rs4986998			+		+													
RAD52	rs11226									+									
TPMT	rs1142345			+															

*The designations are the same as in **Table 2**.

Table 3. The associations between polymorphisms and clinical outcomes observed in Russian (R) and Yakut (Y) patient groups (the second stage of the study)*.

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outcome (i.e., individuals with CT and TT genotypes at rs1800566 showed reduced survival compared to CC homozygotes) [47, 48]. The same correlations were observed in our study. Taking into account the key role of NQO1 in preventing the formation of reactive semiquinone radicals and generating reactive oxygen species (ROS) via redox cycling, one can propose that the worse survival of carriers of CT and TT genotypes is at least the consequence of a chronically elevated level of ROS, which results in enhanced ROS-mediated DNA damage, increased genetic instability, and further cancer progression [47].

In addition to *CDKN1B*, SNPs in *CYP1A1* (T/C, rs4646903) and *CYP1A2* (C/T, rs2470890) were found to also be associated with survival, particularly with OS, in Yakut patients (P = 0.007 and P = 0.0072, respectively). In each case the longer OS occurred in patients with homozygous genotypes TT. In contrast to TPMT and NQO1, the role of CYP1A1 and CYP1A2 in cisplatin metabolism or toxicity is difficult to discern. At the same time, it cannot be excluded that the observed associations are related to metabolic pathways of drugs used in the second and subsequent lines of the chemotherapy (taxanes and anthracyclines).

Totally, 16 SNPs were associated with the side effects of chemotherapy. Thirteen such SNPs were revealed in the Russian group and three SNPs in Yakuts (**Table 3**). A total of 6 of 13 SNPs were associated with an incidence of severe neutropenia in Russian patients. A strong association was estimated for SNP rs1052536 in *LIG3*. Carriers of its homozygous genotype CC had more than 20-fold higher risk of grade 3 or 4 neutropenia than patients with other genotypes (OR = 23.211, 95% CI =2.976–181.02, $P = 2 \times 10^{-6}$). However, the most significant was SNP rs3219484 in *MUTYH*. The SNP was represented by only two genotypes, and patients who carried a heterozygous genotype AG had very low (actually unobserved) risk of developing severe neutropenia (OR = 0.013, 95% CI 0.000–0.220, $P = 4 \times 10^{-8}$). *MUTYH* encodes a DNA glycosylase involved in repair of oxidatively damaged DNA, in particular by excising adenines misincorporated opposite 7,8-dihydro-8-oxoguanines. Such mispairs are promutagenic, and if left unrepaired before the next round of replication, they can give rise to CG → AT transversion mutations [49]. The observed association may reflect the substantial contribution of oxidative stress (i.e., ROS) into cisplatin-induced cytotoxicity. On the other hand, an associative grouping of *MUTYH* SNPs together with SNPs from other DNA repair genes, particularly *RAD52* and *ERCC5*, may also indicate a role of MUTYH in the repair of cisplatin-produced DNA lesions (e.g., participation in detection of the lesions) [50].

Another side effect for which multiple associations were found in the Russian group was anemia. SNPs in *NAT2*, *GSTA4*, *CCNH*, and *EPHX1* genes were associated with the toxicity (**Table 3**). The most significant was SNP rs1801280 in *NAT2*. Cases of anemia occurred more frequently among patients with the heterozygous CT genotypes (78.4%) compared with the homozygous variants (OR = 5.945, 95% CI 2.351–15.031, P = 0.00009). This association is of particular interest because there is no information about a role of NAT2 in the metabolism or toxicity of cisplatin or cyclophosphamide (the second drug in our chemotherapy regimen) [51]. One can propose that the association found is due to linkage between the SNP with a functional SNP(s) in other gene(s). Unlike *NAT2*, three other genes (i.e., *GSTA4*, *CCNH*, and *EPHX1*) are more relevant to the effects of intracellular processing of cisplatin. The cyclin encoded by *CCNH* is a part of a TFIIH complex that is an essential component of a nucleotide excision repair pathway, widely accepted as a main player in removing platinum-DNA adducts from DNA molecules [52].

GSTA4 plays an important role for the detoxification of 4-hydroxynonenal [53], a toxic product of lipid peroxidation, increasing immensely under oxidative stress conditions (e.g., overproduction of ROS), including cisplatin treatment [54, 55]. The role of epoxide hydrolases (EPXHs) in cisplatin-induced toxicity appears to be also related to the effects of oxidative stress. However, in contrast to GSTA4, EPXHs role is inhibitory and results from the abilities of epoxide hydrolases to metabolize epoxyeicosatrienoic acids (EETs) possessing multiple functions, particularly anti-inflammatory effects. The data about relationships between EET hydrolysis and cisplatin toxicity have been mainly obtained from the studies of cisplatin nephrotoxicity [56, 57]. It has been shown that the anti-inflammatory effect of EETs substantially depends on EPHX2, a cytosolic partner of EPHX1. EPHX1 also accepts EETs, although generally to a much lesser extent than EPHX2 [58]. Therefore, a role for EPHX1 in cisplatin toxicity should not be excluded, particularly because of its high expression in kidneys. The association between the SNP rs1051740 in *EPHX1* and nephrotoxicity of the regimen used supports this suggestion.

Three SNPs in *APEX1* (rs1048945), *MSH3* (rs26279), and *MSH6* (rs1042821) were associated with ototoxicity, thrombocytopenia, and emesis in Russian patients (**Table 3**). *APEX1* gene encodes apurinic/apyrimidinic endodeoxyribonuclease 1 playing an essential role in the DNA base excision repair pathway, where it removes apurinic/apyrimidinic sites produced during the repair of bases modified by ROS, alkylating agents, or ionizing radiation [59]. High *APEX1* expression has been associated with a poor outcome for chemoradiotherapy, poor complete response rate, shorter local relapse-free interval, poorer survival, and high angiogenesis [59]. At the same time, a role for APEX1 in protection against toxicity, particularly neurotoxicity, induced by ionizing radiation, and cisplatin treatment, has also been demonstrated [60–62]. ROS and oxidative DNA damage induced by them were shown to be important components of the deleterious effects of cisplatin on neuronal cells. Taking into account the proposed role of ROS in the mechanism of cisplatin-induced hearing loss [63], a contribution of APEX1 can also be hypothesized.

The protein products of *MSH3* and *MSH6* are essential components of the DNA mismatch repair system (MMR). The presence of MMR is thought to be important in mediating cisplatin and carboplatin cytotoxicity, whereas its deficiency, by contrast, may contribute to desensitization of cancer cells to the drugs [64, 65]. In our study, SNPs in *MSH3* and *MSH6* were not associated with tumor response or survival. Nevertheless, patients with minor alleles of the SNPs rs26279 and rs1042821 were at higher risk of thrombocytopenia and emesis, respectively.

Only one gene from the list above was also present among the genes whose polymorphisms were associated with the adverse reactions in Yakut patients, namely, *EPXH1* gene. However, it was associated with a different side effect (i.e., ototoxicity). Furthermore, the corresponding polymorphisms were also different (A/G, rs2234922 and C/G, rs2260863) (**Table 3**). Higher risk of ototoxicity was observed in patients with the most frequent genotypes AA and CC (OR = 26.26, 95% CI 1.502–458.98, P = 0.0005). Although the role of EPXHs in cisplatin toxicity has been mainly associated with their effects on cisplatin-induced kidney injury, the observed link between the *EPHX1* polymorphism and cisplatin ototoxicity can be due to similarity of mechanisms underlying cisplatin-induced hearing impairment and renal dysfunction [66].

The second gene whose allelic variants were associated with a side effect of chemotherapy in Yakut patients (i.e., severe emesis) was *NBN* (G/A, rs1063045). The risk factor for the development

of severe emesis in patients was their heterozygous status at the rs1063045 locus. The protein encoded by *NBN* gene is an important component of the system repairing DNA double-strand breaks that can be induced by different environmental and endogenous agents, including cisplatin. The existing data suggest connections between polymorphic variants of the *NBN* gene and the results of cisplatin-based chemotherapy [67].

Intergroup comparison of genotypes generated with the microarrays revealed substantial differences in population frequencies of alleles and genotypes for many polymorphic markers. More than half of all markers differed significantly in the occurrence of their allelic variants in Russian and Yakut patients.

The proportion of significant genotype frequency differences resembled the results obtained in the first part of the study where a smaller number of polymorphic markers was involved (**Table 2**). Furthermore, the results of the comparisons of population-related associative spectra were also the same: there were no identical correlations for any of significant polymorphisms. All associations between the polymorphic markers and clinical outcomes were specific for each of the ethnic group studied.

These findings are generally compatible with the results of the HapMap project studying of the toxicity of platinum compounds (i.e., cisplatin and carboplatin) to lymphoblastoid cell lines from three groups of racially different individuals [19]. One can propose that the failure to detect common associations/commonly associated polymorphisms in our two groups was due to distinctive ethnic-related characteristics in the molecular mechanisms determining the sensitivity of patients to platinum drugs. Hence the difference in platinum drug sensitivity might not exclusively depend on the difference in variant frequencies of given polymorphisms. Another, but not exclusive, explanation of the findings could be a limitation of the number of polymorphisms tested and a possible omission of other potentially important markers. The latest may be mainly due to the misunderstanding of molecular phenotype(s) of the particular drug(s) [68]. The more relevant is the molecular phenotype, the higher is the potential to optimize the use of a particular drug. For some drugs, such as fluorouracil, irinotecan, and mercaptopurine, some relevant variants (i.e., *DPYD*2A*, *DPYD* 2846T/A, and *TYMS* 2R/3R; *UGT1A1*28* and *UGT1A1*6*; *TPMT *2, TPMT *3A*, and *TPMT*3C*) have been established but for other ones, including platinum-containing agents, they are less apparent [68, 69].

The importance of DNA repair, particularly nucleotide excision repair, for platinum cytotoxicity is widely accepted [64]. However, the overall contribution of even the most common genetic variants to predictions of response to platinum-based therapy is not yet well established [70, 71]. In principle, the situation with other "canonical" pathways affecting mainly cisplatin pharmacokinetics could be described the same way [72]. Therefore, the role of additional mechanisms that are not directly related to cisplatin cellular processing has also been proposed [73]. The results of our study overrepresented with the associations with polymorphisms in genes for different metabolic enzymes (*TPMT, NQO1, EPXH1*, etc.) supports the suggestion (the associations would remain significant even if they were adjusted with the Bonferroni method). The abundance of associations with genes involved in processing of

ROS or ROS-mediated lesions is of particular interest. First, it can point to the higher potential of ROS in total cisplatin-related cytotoxicity [66, 73]. Second, it has been proposed that populations from different geographic regions possess a difference in efficiency of coupling mitochondrial oxidation with phosphorylation, with more heat production and lower ROS generation in North/Northeastern Asians [74, 75]. Consequently, we can expect in Asians lower ability to utilize extra ROS and higher sensitivity to effects of platinum-based drugs. However, because of the relatively small sample sizes and limited number of markers tested, further studies are required to confirm this hypothesis.

In summary, comprehensive exploration of genotypes of polymorphisms in more than 100 genes in ovarian cancer patients from Russian and Yakut ethnic groups, receiving cisplatin-based chemotherapy, revealed pronounced differences in associative spectra between them. Taken in the context of absence of correlations between the associations and polymorphic genotype frequencies, the differences suggest a potential for distinct ethnic-related molecular mechanisms determining the sensitivity of patients to platinum drug effects. The mechanisms are thought to be associated with activity of different metabolic enzymes, including those involved in processing the reactive oxygen species. These genetic findings and differential responses to platinum-based chemotherapy between ethnic groups suggest that future genetic testing may be invaluable not only in predicting chemotherapy response but also in deciding the most appropriate chemotherapy regimen. It may be possible to identify in detail the susceptibility differences to chemotherapy sensitivity at the molecular level and harness this for therapeutic gains.

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