Exp Oncol 2021
43, 4, 336–340

Experimental ONCOLOGY

*CYP2C19*2* GENE VARIANT (G681A, RS4244285) AS A PROGNOSTIC MARKER FOR THE CLINICAL COURSE OF MULTIPLE MYELOMA

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***Background*: Multiple myeloma (MM) is the most common type of paraproteinemic hemoblastosis, which is characterized by an aggressive course, high mortality and a large number of complications. The G681A variant (*2, rs4244285) of the *CYP2C19* gene leads to the formation of an inactive enzyme and, as a consequence, may affect the development and course of MM. *The aim* of this research was to analyze the effect of the G681A variant of the *CYP2C19* gene on the risk of the development of MM and its course. *Materials and Methods:* The study enrolled 158 patients with MM, who underwent standard clinical and laboratory studies: cytological, general clinical, biochemical, as well as molecular cytogenetic and molecular genetic. Cytogenetic analysis of chromosome abnormalities was performed using interphase fluorescence *in situ* hybridization. Genotyping by the G681A variant of the *CYP2C19* gene was performed by polymerase chain reaction-restriction fragment length polymorphism. *Results:* No association was found between the G681A variant of the *CYP2C19* gene and the risk of developing MM. The association between the presence of the *G* allele and *GG* genotypes with significant changes in clinical and biochemical parameters (plasma cell count, α2-globulin, calcium content) in MM patients has been established. In the presence of the *G* allele of the *CYP2C19* gene, the development of chromosomal rearrangements del(13q14.2) or del(13q34) with significantly increased levels of albumin occurs more frequently. *Conclusions:* The G681A variant of the *CYP2C19* gene does not affect the risk of developing MM, but it is associated with significant changes in the clinical and biochemical parameters that determine the severity of the disease and its prognosis. Further research is important to develop new target strategies and maintenance therapy for carriers of different variants of the *CYP2C19* gene (G681A).**

***Key Words*: multiple myeloma, *CYP2C19*, G681A, chromosomal rearrangements, plasma cells.**

DOI: 10.32471/exp-oncology.2312-8852.vol-43-no-4.16924

Multiple myeloma (MM) is the most common form of paraproteinemic hemoblastosis accounting for 1.0–1.8% of all cancer cases. The recent studies indicate a high incidence of this disease in Europe — 4.5–6.0 cases per 100.000 population per year. MM is an incurable disease characterized by an aggressive course, high mortality, and a large number of complications. There is a clear tendency of "rejuvenation" of the disease, and in increasing frequency, the clinical presentation occurs at the age of up to 40 years. Despite significant advances in treatment, only 10–15% of patients achieve the expected survival, which requires new research for the prognosis of the disease course [1, 2].

In recent years, data have been obtained to confirm that a functionally significant polymorphism of genes encoding enzymes of the biotransformation system of xenobiotics is one of the important factors in the development and progression of malignant neoplasms, including MM [3]. The CYP2C19, an isoenzyme of cytochrome P450, which plays an important role in both detoxification or inactivation of potential carcinogens and in the activation of some environmental procarcinogens and the formation of functionally active DNA-binding metabolites such as nitrosamines, and therefore may be involved in the formation of oncological pathology [4].

The *CYP2C19* gene (OMIM*124020) is located on chromosome 10q23.33. Among the gene variants, the G681A variant (allelic variant *2, rs4244285) is the most significant and widespread. It is formed under the substitution of guanine with adenine at position 681 of exon 5, which leads to the formation of an aberrant splicing site. The creation of this site shifts the reading frame of mRNA, starting with 215 amino acid residues, and prematurely creates a stop codon for 20 amino acid residues earlier, resulting in a shorter, functionally inactive protein [5]. To date, the association of this variant of *CYP2C19* with the risk of developing various cancers — oral cancer, breast cancer, cancer of digestive tract, etc., has been detected [4, 6, 7]. However, studies on the association of the *CYP2C19* gene variant (G681A) with the risk of developing MM have not yet been performed. The aim of this research was to analyze the effect of the

Submitted: June 15, 2021.

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Abbreviations used: i-FISH – interphase fluorescence *in situ* hybridization; LDH – lactate dehydrogenase; MM – multiple myeloma; PCR-RFLP – polymerase chain reaction with restriction fragment length polymorphism.

G681A variant of the *CYP2C19* gene on the development and course of MM.

MATERIALS AND METHODS

The study enrolled 158 patients with MM — 81 women (51.3%) and 77 (48.7%) men who underwent treatment at the Oncohematology Department of Kyiv Centre of Bone Marrow Transplantology in 2014–2018. The average age of the patients was 53.71 ± 9.38 years, of which the average age of women was 54.44 ± 9.79 years, and men — 53.00 ± 8.98 years.

Patients were examined in terms of a wide range of standard clinical and laboratory studies, which included cytological, general clinical, biochemical, and molecular cytogenetic methods of examination according to the protocol of the Ministry of Health of Ukraine [8]. Cytological examination to determine the level of plasma cells in the bone marrow is one of the main clinical markers of MM [8]. It was performed using a unified method for differentiation of formed elements in stained smears of the bone marrow puncture samples.

The general clinical studies included tests for the presence of protein in the urine and the presence of Bence-Jones protein in the urine. Biochemical methods were used to determine the levels of creatinine (μmol/l), calcium (mmol/l), and lactate dehydrogenase (LDH) (U/l). Calcium concentration studies were performed using the Calcium-Arsenazo reagent kit (ELITechGroup, France), creatinine concentration was determined using the Creatinine JAFFE reagent kit (ELITechGroup, France), and LDH levels were determined using the LDG-L SL kit (ELITechGroup, France). All studies were performed on the automatic analyzer SelectraPRO M (Netherlands).

Detection of protein fractions in serum and 24-h urine was performed by the method of electrophoretic separation of proteins on the agarose film SAS-MX100100 (Helena Biosciences Europe, United Kingdom) in the electrophoresis chamber Helena Biosciences SAS-MX (Helena Biosciences Europe, United Kingdom). The separated proteins were fixed with a mixture of acid/alcohol solutions and then stained with acid blue dye. After decolorization and drying, the gels were interpreted using the Platinum III program. Gels SAS-MX100100 allow us to clearly divide serum proteins into 5 fractions: albumin (%/g/l), alpha-1 globulins (%/g/l), alpha-2 globulins (%/g/l), beta globulins (%/g/l), gamma globulin (%/g/l). Due to the high-resolution ability of the plates, the presence of monoclonal proteins can be detected. Immunofixation was used to confirm the presence of monoclonal proteins and their identification.

Cytogenetic analysis of chromosome abnormalities was performed using interphase fluorescence *in situ* hybridization on glass (i-FISH). i-FISH studies were performed on interphase cell nuclei after long-term (96-h) cultivation of bone marrow or peripheral blood cells in the RPMI 1640 medium with the addition of 20% inactivated fetal calf serum and 0.97% gentamicin. The following kits were used to visualize the rearrangements: Deletion-Probe XL DLEU/LAMP (13q14.2/13q34) — Fig. 1, XL P53 (17p13); to detect Dual Fusion Probe translocations: XL t(4;14) (t(4;14)(p16;q32) FGFR3/IGH), XL t(6;14) (t(6;14)(p21;q32) CCND3/IGH), XL t(11;14) (t(11;14)(q13;q32) CCND1/IGH), XL t(14;16) (t(14;16)(q32;q23) IGH/MAF/WWOX) (MetaSystems, Germany).

For molecular genetic analysis, DNA was isolated from the peripheral blood samples using the Quick-DNA Universal Kit (Zymo Research, USA) according to the instructions. Genotyping by the G681A variant of the *CYP2C19* gene was performed according to a modified protocol using the polymerase chain reaction method and subsequent analysis of restriction fragment length polymorphism (PCR-RFLP) [9]. The DNA fragments of the *CYP2C19* gene were amplified using the commercial DreamTaq Green PCR Master Mix kit (Thermo Fisher Scientific, USA) and specific oligonucleotide primers (Metabion, Germany) in compliance with the conditions of the reaction. The amplification products of DNA fragments were subjected to hydrolytic cleavage by restriction endonuclease *SmaI* (Thermo Fisher Scientific, USA). PCR-RFLP products with the sizes of 118 bp and 49 bp corresponded to the GG genotype, and with the size of 167 bp — to the AA genotype, respectively; fragments of 167 bp, 118 bp, and 49 bp corresponded to the GA genotype of the *CYP2C19*2* allelic variant (Fig. 2).

All patients gave informed consent to participate in the study, and permission was obtained from the Bioethics Committee of P.L. Shupyk National Medical Academy of Postgraduate Education (№ 4 as of 07 April, 2014).

Statistical data processing was performed using Microsoft Excel Pro Plus 2016 and SPSS v.27 software.

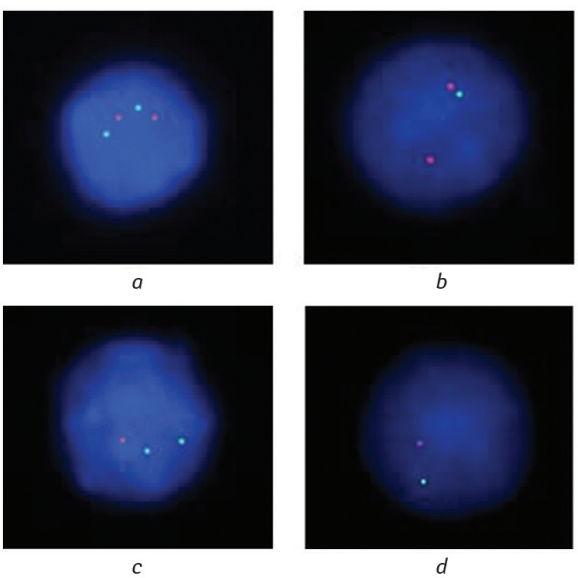

Fig. 1. Variants of the distribution of luminescence signals of loci on the long arm of chromosome 13: green signal — 13q34 (LAMP), red signal — 13q14.2 (DLEU); *a* — normal signal distribution; *b* — del(13q34); *c* — del(13q14.2); *d* — del(13q14.2) and del(13q34)

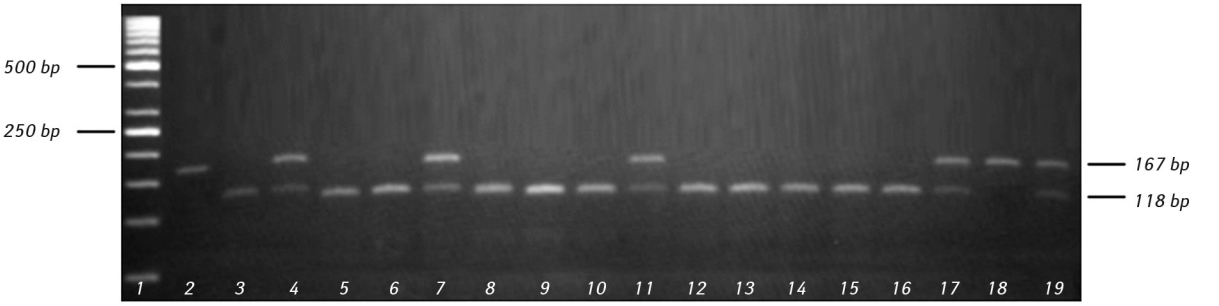

Fig. 2. Electrophoregram of PCR-RFPF products of the G681A variant of the *CYP2C19* gene in MM patients: 1 — molecular weight marker, samples 3, 5, 6, 8-10, 12-16 — the GG genotype, samples 4, 7, 11, 17, 19 — the GA genotype, samples 2, 18 — the AA genotype

In the analysis of the basic clinical characteristics, the mean value ± standard deviation was calculated. Genotype and allele frequencies in the study and comparison groups were compared using the $\chi 2$ test. The studied parameters were checked for the normality of distribution using the Kolmogorov — Smirnov test. In the case of a normal distribution, the significance of the differences in the parameters was determined using Student's *t*-test, and in a distribution that differed from the normal one, the Mann — Whitney U-test was used. Differences were considered significant for all types of analysis at $p < 0.05$.

RESULTS

The molecular genetic analysis for the distribution of the *CYP2C19 (G681A*) gene variants yielded the following genotype distribution frequencies in the MM group: the GG genotype was detected in 72.3%, the GA genotype — in 23.9%, and patients with the AA genotype amounted to 3.2%. The frequency of genotypes in the MM group corresponded to the Hardy–Weinberg equilibrium. We analyzed and compared the obtained frequencies of genotype distribution with the frequencies characterizing the European population, which were taken from the open database of the "1000 Genomes" project and with the frequencies for the Ukrainian population, obtained in the study by N.M. Levkovych (Table 1) [10, 11]. The frequencies of the obtained genotypes according to the G681A polymorphic variant of the *CYP2C19* gene in the examined groups did not differ significantly from the general population frequency of the genotype distribution for Europe and Ukraine. The results indicate that the G681A variant of the *CYP2C19* gene does not affect the risk of developing MM.

Subsequently, we analyzed the obtained average levels of clinical and biochemical parameters in the examined patients with MM, which are shown in Table 2. These results correspond to the generally accepted descriptions of the clinical presentation of MM: the presence of specific plasma cells in the blood, elevated creatinine and LDH due to kidney damage (myeloma nephropathy), elevated (the upper limit of normal) calcium levels due to bone destruction.

When comparing the results of genetic testing and the listed clinical and biochemical parameters that determine the stage of the disease and predict its course, we found significant differences (Table 3). Having divided patients into subgroups by genotypes, we found that in some cases the parameters between the subgroups differed significantly. Thus, in the general group, there was a significant difference between the genotypes: GG *vs* AA, GA *vs* AA and GG *vs* GA+AA in terms of the level of plasma cells; between the genotypes: GG *vs* GA and GG *vs* GA+AA in terms of the level of α2-globulin; between the GG and GA genotypes in terms of calcium level. There was no significant difference between the subgroups in terms of creatinine, β2-microglobulin, LDH, and albumin.

According to the results of cytogenetic analysis, it was found that in patients with MM, the frequency of detected chromosomal abnormalities was as follows: del(13q14.2) — 12.5%, del(17p13) — 7.4%, del(13q34) — 18.4%, t(4:14)(p16:q32) — 12.5%, t(11;14) — 10.0%, t(14:16) — 10.4%.

No significant differences were found when analyzing the distribution of genotypes in terms of the G681A variant of the *CYP2C19* gene in the subgroups of MM patients with detected chromosomal abnormalities and without them. When further comparing the results — the existing chromosomal abnormalities with clinical and biochemical parameters in patients with MM, we found a significant difference ($p < 0.05$) for the average level of albumin (Table 4).

When expanding this analysis and taking into account alleles in terms of the G681A variant of the *CYP2C19* gene, in addition to chromosomal abnormalities, it was found that in the presence of a combination of del(13q14.2) or del(13q34) and the G allele of the *CYP2C19* gene, the average albumin level was signifi-

Table 1. Analysis of the frequency distribution of genotypes by the G681A polymorphic variant of the *CYP2C19* gene in the comparison groups

Genotype, allele	Patients with MM n (%)	European population n (%)	Ukrainian population n (%)
GG	115 (72.7)	363 (72.2)	706 (76.9)
GA	38 (24.1)	134 (26.6)	194 (21.1)
AA	5 (3.2)	6 (1.2)	18 (2.0)
G	0.85	0.85	0.87
A	0.15	0.15	0.13

Table 2. Clinical and biochemical parameters in the examined MM patients

Diagnostic indicators	Average value
Plasma cells, %	35.35 ± 22.17
Creatinine, μmol/l	143.75 ± 139.09
Calcium, mmol/l	2.42 ± 0.42
LDH, u/l	313.12 ± 195.97
Albumin, g/l	34.61 ± 7.24
α2-globulin, g/l	7.96 ± 2.94
β2-microglobulin, mg/l	7.34 ± 6.52

Table 3. The average values of clinical and biochemical parameters in MM patients depending on the G681A variant of the *CYP2C19* gene

Clinical and biochemical parameters	GG	GA	AA	GA+AA
Plasma cells,%	34.57 ± 21.61[1, 2]	32.95 ± 23.03[1]	61.91 ± 13.78	36.46 ± 23.96
Creatinine, μmol/l	141.11 ± 142.71	162.71 ± 142.81	102.58 ± 34.99	154.12 ± 134.15
α2-globulin, g/l	7.40 ± 2.64[2, 3]	9.57 ± 3.38	8.61 ± 1.73	9.43 ± 3.12
β2-microglobulin, mg/l	6.59 ± 6.24	9.81 ± 7.30	3.88 ± 1.89	8.56 ± 6.94
Calcium, mmol/l	2.29 ± 0.36[3]	2.58 ± 0.56	2.41 ± 0.22	2.55 ± 0.52
LDH, u/l	311.15 ± 177.97	309.95 ± 236.94	235.72 ± 111.52	297.15 ± 220.70
Albumin, g/l	34.65 ± 7.65	35.23 ± 6.21	31.58 ± 6.11	34.71 ± 6.24

Note: [1]$p < 0.05$ compared with AA, [2]$p < 0.05$ compared with GA+AA, [3]$p < 0.05$ compared with GA.

Table 4. The average level of albumin (g/l) in MM patients depending on the presence of chromosomal abnormalities

Chromosomal abnormality		Average albumin level, g/l
del(13q14.2)	Yes	38.85 ± 4.54*
	No	32.38 ± 5.68
del(13q34)	Yes	39.00 ± 5.62*
	No	32.19 ± 6.32

Note: The data are presented as mean ± SD; *compared with patients without chromosomal abnormalities, $p < 0.05$.

Table 5. The average level of albumin (g/l) in MM patients depending on the presence of chromosomal abnormalities and alleles in terms of the G681A variant of the *CYP2C19* gene

Genetic variant / Chromosomal abnormality		*CYP2C19* G allele	*CYP2C19* A allele
del(13q14.2)	Yes	42.70 ± 1.41 g/l*	35.01 ± 0.86 g/l *
	No	32.36 ± 6.14 g/l	32.42 ± 5.27 g/l
del(13q34)	Yes	42.50 ± 4.89 g/l*	34.34 ± 1.31 g/l *
	No	32.34 ± 6.71 g/l	31.89 ± 5.90 g/l

Note: The data are presented as mean ± SD;*compared with patients without chromosomal abnormalities, $p < 0.05$.

cantly higher in patients with MM as compared to patients without chromosomal abnormalities (Table 5).

DISCUSSION

For historical reasons, variants of the *CYP2C19* gene, including the G681A variant, have previously been studied only as pharmacogenetic markers. In MM patients, in particular, the effect of the G681A variant of the *CYP2C19* gene on the efficacy of antitumor agents thalidomide and bortezomib has been studied. It was hypothesized that patients with the AA genotype should have a worse response to therapy with these medications due to the reduced enzyme activity. However, a large number of studies have not confirmed this hypothesis [12, 13]. At the same time, in parallel, it was found that there is an association between the G681A variant of the *CYP2C19* gene and the risk of developing other cancers and their unfavorable course [4, 6, 7]. This effect was explained based on the hypothesis of the influence of environmental procarcinogens on the pathogenesis of malignant tumors [14].

The results of our study indicate that the G681A variant of the *CYP2C19* gene does not affect the risk of developing MM. We did not find such associations in the available literature. However, we demonstrated a number of significant differences between the clinical and biochemical parameters characterizing the disease and the prognosis for its course, and genotypes of the studied variant of the *CYP2C19* gene, namely a significant decrease in plasma cells, along with an increase in α2-globulin and calcium. In the study by Vangsted *et al*. [15], the association of genotypes with biochemical parameters, in particular, creatinine levels, has also been shown. In contrast, in the study by Zhou *et al*. [16], no significant difference has been found between the biochemical parameters and genotypes in terms of the G681A variant of the *CYP2C19* gene.

In our previous study, which examined the effect of gene variants of the second detoxification phase of xenobiotics and medicines on the risk of developing the refractory forms of MM, we elaborated a prognostic model for the risk of developing the refractory forms of MM, which, in addition to the deletion variant of the *GSTM1* gene, included the level of calcium and α2-globulin [17]. It has been suggested that α2-globulin levels represent an indirect marker of kidney damage. In this study, we found that it was elevated in the presence of GA and GA+AA genotypes of the *CYP2C19* gene, whereas carriers of GA genotype presented with elevated calcium levels. The identified features provide evidence of an unfavorable course of the disease in patients with a minor allele of the *CYP2C19* gene in the homo- or heterozygous state. This is obviously confirmed by the significantly highest level of plasma cells in carriers of the AA genotype. It is well known that elevated plasma cell levels are a marker of a severe course of MM [17].

In this study, we did not identify associations between the G681A variant of the *CYP2C19* gene and the presence of chromosomal abnormalities in patients with MM. However, we have shown that in the presence of the G allele in terms of the *CYP2C19* gene, the clinical manifestation is significantly more often accompanied by the development of chromosomal rearrangements del(13q14.2) or del(13q34) and elevated levels of albumin. Hence, although according to the national protocol, chromosomal abnormalities del(13q14.2) or del(13q34) refer to intermediate risk, the literature provides the results of studies that indicate a «protective» effect against adverse events in case of the presence of chromosomal abnormalities in MM patients [18]. The results of our study indicate that patients with del(13q14.2) or del(13q34) and the G allele of the *CYP2C19* gene had much and significantly higher levels of albumin, which is an important prognostic biochemical marker of a more susceptible course of MM. Some authors have proposed to calculate the ratio of globulin and albumin fractions as a predictor of mortality in the cohort of MM patients [19].

Therefore, we can conclude that the G681A variant of the *CYP2C19* gene is not associated with the risk of developing MM but affects some important clinical and biochemical parameters that determine the stage of the disease and its severity, namely plasma

cell count, α2-globulin and calcium calcium. In the presence of the G allele of the *CYP2C19* gene, chromosomal rearrangements del(13q14.2) or del(13q34) with significantly increased levels of albumin are more frequent. Further research is important to develop new target strategies and maintenance therapy for carriers of different variants of the *CYP2C19* gene (G681A).

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ВАРІАНТ ГЕНА *CYP2C19*2* (G681A, RS4244285) ЯК ПРОГНОСТИЧНИЙ МАРКЕР КЛІНІЧНОГО ПЕРЕБІГУ МНОЖИННОЇ МІЄЛОМИ

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Стан питання: Множинна мієлома (ММ) — найпоширеніша форма парапротеїнемічних гемабластозів, яка характеризується агресивним перебігом, високим рівнем смертності та великою кількістю ускладнень. Варіант *G681A* (*2, rs4244285) гена *CYP2C19* призводить до утворення неактивного ферменту, і як наслідок, може впливати на розвиток та перебіг ММ. ***Мета:*** Проаналізувати вплив варіанта G681A гена *CYP2C19* на ризик розвитку та перебіг ММ. ***Матеріали та методи:*** У дослідженні взяли участь 158 пацієнтів з ММ, у яких було проведено стандартні клініко-лабораторні дослідження: цитологічні, загальноклінічні, біохімічні, а також молекулярно-цитогенетичні та молекулярно-генетичні. ***Результати:*** Не виявлено асоціації між варіантом G681A гена *CYP2C19* та ризиком розвитку ММ. Встановлено асоціацію наявності алеля *G* та генотипів *GG* зі значущими змінами клініко-біохімічних показників (плазматичних клітин, α2-глобуліну, кальцію) у пацієнтів з ММ. За наявності G-алелю за геном *CYP2C19* у пацієнтів з ММ клінічна маніфестація частіше супроводжується розвитком хромосомних перебудов del(13q14.2) або del(13q34) зі значуще підвищеним рівнем альбуміну. ***Висновки:*** Варіант G681A гена *CYP2C19* не впливає на ризик розвитку ММ, але асоційований зі значущими змінами провідних клініко-біохімічних показників, що визначають тяжкість захворювання та прогноз. Подальші дослідження важливі для розробки нових таргетних стратегій та підтримувальної терапії для носіїв різних варіантів гена *CYP2C19* (G681A).

Ключові слова: множинна мієлома, *CYP2C19*, G681A, хромосомні перебудови, плазматичні клітини.