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The Association of *ABCC5* and *ABCC11* Polymorphisms with The Pharmacokinetics of 5-FU in Advanced Gastric Cancer Patients

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ABSTRACT

Objective: Gastric cancer is the second leading cause of cancer-related deaths worldwide. 5-Fluorouracil (5-FU) is one of the most commonly used drugs to treat cancer, but 5-FU and its forms are characterized by wide inter-individual pharmacokinetic variability. *ABCC5* and *ABCC11* are members of the ABC transporter superfamily and play a role in the efflux of antineoplastic drugs like 5-FU.

Methods: The influence of two SNPs in *ABCC5* (rs562, *T>C*) and *ABCC11* (rs17822931, *G>A*) was evaluated based on the pharmacokinetics and toxicity of 5-FU in HER2-negative advanced gastric cancer patients treated with cisplatin and 5-FU (n=18). The genetic variants and plasma 5-FU concentrations were detected by RT-PCR and HPLC, respectively.

Results: There was no statistically significant difference between 5-FU $AUC_{0\text{-}96\ h}$ values and *ABCC5* (rs562; *T>C*), 21.04 ±3.46 vs 16.65 µg.h/mL, *p*=0.261 and *ABCC11* (rs17822931; *G>A*), 17.04 ±4.39 vs 54 ±3.79 µg.h/mL, *p*=0.564 variants. Similarly, there were no statistically significant differences between the variants and the most frequently observed side effects of diarrhea and mucositis.

Conclusion: We recommend investigating the noted SNPs more precisely in a larger study population with more comprehensive evaluation.

Keywords: *ABCC5*, *ABCC11*, 5-FU, pharmacogenetics, gastric cancer

1. INTRODUCTION

Gastric cancer is the fourth most commonly diagnosed type of cancer and the second leading cause of cancer-related deaths worldwide. Surgery is usually the only curative therapy, but most patients are diagnosed with unrespectable, locally advanced, or metastatic disease. Unfortunately, the most common treatment is palliative chemotherapy. Although there is no standard therapy regimen; 5-Fluorouracil (5-FU) and its forms are the backbone of chemotherapy. To improve therapy outcomes, 5-FU is usually given in combination with other antineoplastic agents such as cisplatin, oxaliplatin, and irinotecan. 5-FU is a fluoropyrimidine and antimetabolite drug. It inhibits essential biosynthetic processes and is incorporated into DNA and RNA and thus inhibits their normal function (1–5).

5-FU is generally administered based on the traditional body surface area (BSA) dosing. In the treatment of metastatic or locally advanced gastric cancers, it is commonly given in a dose of 1000 mg/m^2 for 1-4 days using a continuous infusion in combination with cisplatin 75-100 mg/m^2 (6,7).

Like most chemotherapeutics, 5-FU is generally characterized by a narrow therapeutic index and a large inter-individual pharmacokinetic variability that directly affects the efficacy and toxicity. Studies have shown that many patients who are treated with 5-FU are not receiving the appropriate doses to achieve optimal plasma concentrations. Indeed, only 20-30% of patients are treated in the appropriate dose range with approximately 40-60% of patients underdosed and 10-20% of patients overdosed. These findings indicate considerable variability in plasma 5-FU levels resulting in inter-patient pharmacokinetic variability. This in turn leads to differences in the drug-response relationship and contributes to toxicity and treatment failure (8–11).

ABCC5 (MRP5) and *ABCC11* (MRP8) from the MRP class of the ATP-binding cassette (ABC) transporter superfamily are expressed in most human tissues. Whereas ABCC5 is localized on the basolateral membrane, *ABCC11* is located on both the basolateral and apical membranes in polarized cells. They can extrude various exogenous and endogenous compounds in an ATP-dependent manner from the cell. Several studies

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have shown that 5-FU and its active metabolite, 5-FdUMP, are potential substrates for *ABCC5* and *ABCC11* (12,13). Genetic alterations in genes encoding ABC transporters are an important pharmacokinetic-based source for differences in response to antineoplastic drugs including 5-FU. Therefore, genetic differences in genes encoding *ABCC5* and *ABCC11* might be identified as cyclic nucleotide transporters that mediate the cellular efflux of cytotoxic monophosphorylated metabolites of 5-FU .These differences have been associated with 5-FU resistance and may affect the pharmacokinetic behavior of 5-FU and partially account for the differences between individuals (14,15).

This study examined the influence of two single nucleotide polymorphisms (SNPs) in *ABCC5* (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) on the pharmacokinetics and toxicity of 5-FU in HER2-negative advanced gastric cancer patients treated with cisplatin and 5-FU. These results can lead to individualized chemotherapy with 5-FU in patients with (HER2-negative) advanced gastric/gastroesophageal junction cancer.

2. METHODS

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board (Local Clinical Ethics Committee of Istanbul University Cerrahpaşa Medical Faculty, No. 2012-05/A-28).

2.1. Patients

The study group existed of a total 18 male and female patients with HER2-negative advanced gastric – or gastroesophageal junction cancer.

2.1.1. Inclusion criteria

We enrolled patients with recurrent (HER2-negative) gastric cancer with impossible curative surgical resection and who had received no previous chemotherapy other than (neo) adjuvant regimens in the last six months after curative surgical resection. They age range was between 18 and 75 years and performance status between 0-2 according to Eastern Cooperative Oncology Group (ECOG) with no cardiac problems in their history and normal kidney, liver, and bone marrow functions.

2.2.2. Exclusion criteria

We excluded those with the following: other malignancies except *in situ* cervical cancer and basal cell carcinoma; HER2-positive subjects; subjects with active gastrointestinal bleeding, malabsorption, and jejunostomy; patients who previously received (neo)adjuvant treatment and had toxicity events above grade 2.0 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (National Cancer Institute, USA 2017); creatinine clearance above 60 mL/min (calculated with Cockcroft-Gault formula); neutrophil count above $1.5x10^9$/L and thrombocyte count above $100x10^9$/L; serum bilirubin concentrations 1.5 times higher than upper limit of normal; AST and ALT concentrations 2.5 times higher than upper limit of normal; alkaline phosphatase concentrations 2.5 times more than upper limit of normal; serum albumin concentrations above 2.5 g/dL; clinically significant hearing impairment; subjects with known dihydropyrimidine dehydrogenase (DPYD) deficiency; subjects with known or symptomatic brain metastases; serious systemic illnesses (uncontrolled diabetes, congestive heart failure etc.); subjects who have had a surgical procedure in a period of shorter than 4 weeks prior to study entry; subjects who have had radiotherapy for a period less than 4 weeks prior to study entry; and subjects who have had allergy against 5-FU or cisplatin. Pregnant women and those likely to become pregnant were also excluded.

2.2. Treatment and Sample Collection

The patients who met the inclusion criteria and voluntarily participated in the study were treated with a standard therapy plan at Istanbul Cerraspasa University Medical Faculty, Department of Medical Oncology. The therapy plan consisted of the combined administration of cisplatin and 5-FU. Cisplatin (75 mg/m^2) was supplied as intravenous infusion for 2 hr on day 1 of every cycle after hydration and premedication was administered. 5-FU (750-1000 mg/m^2) was supplied as continuous intravenous infusion (CIV) via a port-a-cath on day 1-4 of every cycle after cisplatin administration was completed. The steps were repeated every three weeks for 6 cycles.

The blood samples (5 mL) for genotype analysis were collected in ethylene diamine tetra acetic acid (EDTA) tubes on day 1 of the first cycle. Genomic DNA was isolated from whole blood for genotyping analysis of the *ABCC5* (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) variants at the same time. Before analysis, the DNA samples were stored at +4 °C. The blood samples (6 mL) for quantitative analysis of 5-FU were collected at 24th hr of iv infusion of the first cycle (C_{ss}-steady state concentration) in heparinized tubes and were placed on ice. The samples were centrifuged immediately for 10 min at 3000 rpm and the plasma was separated. The plasma samples were stored at –70 °C until analysis.

2.3. Genotyping Analysis

Genomic DNA was isolated from whole blood using High Pure PCR Template preparation kit (Roche Diagnostics GmbH, Mannheim, Germany). Genotyping of *ABCC5* (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) was performed on real-time PCR platform using a 96-well LightCyler® 480 instrument II system (Roche Diagnostics GmbH, Mannheim, Germany) using hybridization probes and master mix according to the manufacturer's instructions. The features of custom-designed LightSNiP assay probes are summarized in Table 1.

Table 1. *Features of custom-designed LightSNiP assay probes.*

Gene	Position	Alleles	Reference Sequence	Melting Temperature
ABCC5 **(rs562)**	chr3:183920057	*T>C*	CACgACATgCAACgCTgACCATTCAA[C/T] TgATgACAgCAgTgACCACgCCCAC	57.62 °C for *T* 65.35 °C for *C*
ABCC11 **(rs17822931)**	chr16:48224287	*G>A*	AgTggTTCAgACggTgAATgACCg[g/A] CTCATgTgACCgTTACgTCTTCgTC	55.54 °C for *A* 65.11 °C for *G*

rs: reference SNP number; alleles in the square brackets indicates the polymorphisms.

The 1X FastStart DNA Master Mix, 2 mM $MgCl_2$, 0.2 mM LightSNP HybProbe, PCR-grade water, and 500 ng DNA sample was added to each sample at a final volume of 20 µL reaction mix. The run was repeated in a different day with three randomly selected DNA samples for assay control, and PCR-grade water was used for negative control. Each genotype was determined according to the melting curve analysis of the related allele by the Carousel Based System PCR program (16).

2.4. Pharmacokinetic Analysis

A validated High Performance Liquid Chromatography – Ultraviolet and Visible light (HPLC-UV/VIS) method by Casale et al. was used for the determination of 5-FU in plasma (17).

2.4.1. Chemicals

5-FU 1000 mg/20 mL solution for injection (Batch 1919601) was supplied by Kocak Farma Company (Turkey). The 5-bromo-5,6-dihydrouracil (5-BrH_2) was obtained from Sigma-Aldrich (Munich, Germany). Isopropanol and acetonitrile were supplied from Riedel-de Haën (Hanover, Germany). Potassium phosphate tribasic was purchased from Sigma-Aldrich (Munich, Germany). Ammonium sulphate (powder), diethyl ether and other reagents and solvents were supplied from Merck KGaA (Darmstadt, Germany).

2.4.2. Instruments and chromatographic conditions

5-FU and the internal standard (IS) 5-bromo-5,6-dihydrouracil were separated on a 5 µm C18 110 Å, reversed phase column 250 x 4.6 mm (Phenomenex® Gemini®, USA) with a SecurityGuard™ C18 column 4 x 3.0 mm (Phenomenex® Gemini®, USA) operating at a temperature of 35 °C. The mobile phase was a solution consisting of 1.5 mM K_3PO_4 buffer and acetonitrile (99.5:0.5, v:v). The solution was adjusted to pH 4.5 with ortho-phosphoric acid (1 M). The flow rate was 1.0 mL/min, and the eluate was detected at 210 nm wavelength by a Waters 2487® dual λ absorbance detector (USA). Sample injection (50 µL) was performed with an integrated autosampler separations module (Waters® 2695 Alliance, USA). Data were recorded with Empower (Waters, USA), and further calculations used Microsoft Excel (USA).

First, 100 µg/mL of IS was added to 1000 µL of plasma. After brief vortexing, 1000 µL of saturated ammonium sulphate was added to precipitate the proteins. This mixture was again vortexed, and then 4 mL of isopropanol:diethyl ether (80:20, v:v) was added. After 3 minutes of vortex-mixing, the samples were centrifuged for 10 minutes at 4000 rpm. Subsequently, the organic phase was transferred into a clean tube and evaporated to dryness in a 45 °C block heater with sample concentrator (Stuart®, UK), under a nitrogen stream; 500 µL of saturated ammonium sulphate was added again to this residue. After briefly vortexing, 2 mL of isopropanol:diethyl ether (80:20, v:v) was added. Hereafter, the sample is vortex-mixed for 3 minutes and then centrifuged at 4000 rpm for 10 minutes. Subsequently, the organic phase is separated and filtered through a Sartorius PTFE (0.20 µM) filter (Germany) into a clean tube. The content of clean tube was evaporated again to dryness. After evaporating to dryness, the residue was dissolved in 250 µL of mobile phase and vortex-mixed for 3 minutes. The sample was then centrifuged for 5 minutes at 4000 rpm.

2.4.3. Calculation of Pharmacokinetic Parameters

The main 5-FU pharmacokinetic parameters were selected for steady state concentration (C_{ss}) and area under the curve (AUC) analyses. We assumed that samples taken at t=24 resemble the C_{ss} of 5-FU. Subsequently, the AUC was calculated as C_{ss} multiplied by the duration of the infusion (TCI) as follows: AUC = 'C_{ss} x TCI' (18).

2.5. Statistical Analysis

The Hardy-Weinberg equilibrium reports whether the studied population was biased or not using the chi-square (χ^2) test. Mann-Whitney U and Kruskal Wallis tests were used for testing the significance of this relationship between genotype and pharmacokinetics parameters. A *P* value of <0.05 was considered statistically significant.

3. RESULTS

A total of 18 patients with HER2-negative advanced gastric – or gastroesophageal junction cancer were enrolled in the study at Istanbul Cerrahpaşa University, Medical Oncology Department in Istanbul, Turkey. All patients received 5-FU 750-1000 mg/m^2 via continuous intravenous infusion on day 1-4 after intravenous cisplatin 75 mg/m^2 administration for 2 hr on day 1. An overview of the patients' characteristics is shown in Table 2.

Table 2. *Characteristics of the study population.*

Patient Characteristics	
***Age* (years, mean ±SEM)**	59 ±10
***Body surface area* (m^2, mean ±SD)**	1.75 ±0.24
	Number of patients (%)
Gender	
Female	6 (33.33)
Male	12 (66.67)
ECOG performance status	
Grade 1	18 (100)
Body surface area ($m^{2)}$	
Mean ± SD	1.75 ± 0.24 m^2
TNM stage	
Stage 3	1 (5.55)
Stage 4	17 (94.45)
Histopathological diagnosis	
Signet ring cell carcinoma (SRCC)	5 (27.78)
Adenocarcinoma	13 (72.22)

SEM: Standart Error Mean; SD: Standart Deviation; ECOG: Eastern Cooperative Oncology Group

3.1. Genotyping Results

ABCC5 (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) variants were evaluated in patients with HER2-negative advanced gastric – or gastroesophageal junction cancer. All samples (n=18) were genotyped with 100% success rate and concordance. The genotype distributions and features of studied population are summarized in Table 3. The genotype distribution was found to be consistent with the Hardy-Weinberg equilibrium (HWE) model suggesting that the studied population was unbiased. The allele frequencies were found and were notably similar to Europeans as stated in 1000 Genomes Project phase3 release V3+ (ID: 257713) in the NCBI (National Center for Biotechnology Information) SNP database (dbSNP, https://www.ncbi.nlm.nih.gov/snp).

Table 3. *Variant alleles, genotype distribution, minor allele frequencies, and HWE of the studied SNPs.*

SNP	Variant allele	Geno-type	n (%)	Minor allele frequencies	HWE	
					X^2	*p value*
***ABCC5* (rs562)**	*C*	*TT*	2 (11.11)	0.56	2.205	0.562
		TC	12 (66.67)			
		CC	4 (22.22)			
***ABCC11* (rs17822931)**	*A*	*GG*	14 (77.77)	0.11	0.281	0.882
		GA	4 (22.22)			
		AA	0 (0)			

SNP: Single nucleotide polymorphism; rs: reference SNP number; n (%): number (percentage) of patients; HWE: Hardy-Weinberg equilibrium; χ^2: chi-square; p<0.05 indicates statistical significance.

3.2. Pharmacokinetic Results

The pharmacokinetics results were evaluated by examining 5-FU exposure expressed as $AUC_{0\text{-}96h}$ for 18 patients. There was a nearly 10-fold inter-individual variation of 5-FU exposure among patients (4.48 to 49.19 mg.h/L; mean: 20.55 mg.h/L; SD: 13.10 mg.h/L; CV%: 63.74%) (Fig. 1). According to therapeutic window of 5-FU infusion (9), only 23% of patients had an AUC within the therapeutic range (20–30 mg.h/L); 16% of patients had an AUC>30 mg.h/L, and 61% of patients had an AUC<20 mg.h/L. All patients were dosed according to the BSA standard but AUC levels of 5-FU were not correlated with BSA (Pearson's correlation efficiency: 0.2860; *p*=0.250).

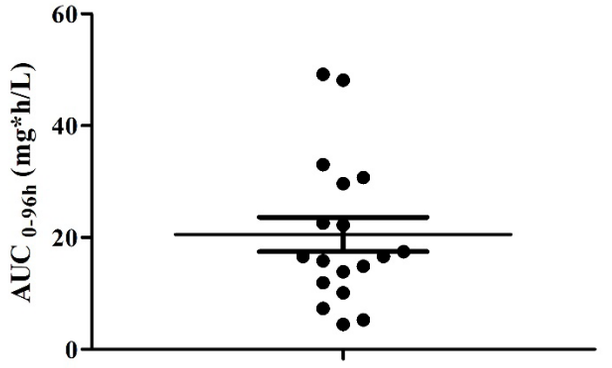

Fig 1. *Comparison of $AUC_{0\text{-}96h}$ patient values of each subject individually in the study group.*

Stomatitis, diarrhea, mucositis, and hand–foot syndrome were considered toxicity events highly-related to 5-FU within the 5-FU and cisplatin regimens. Hand-foot syndrome and stomatitis were not observed in this study group at the end of the 1st cycle of the therapy. Five patients had mucositis and mean 5-FU $AUC_{0\text{-}96h}$ values (28.37 ±19.53 mg.h/L vs 17.54 ±8.98 mg.h/L; *p*=0.119) were higher in patients with mucositis. Only three patients had grade 2 diarrhea. Mean 5-FU AUC values (33.22 ±15.86 mg.h/L vs 18.02 ±11.06 mg.h/L; *p*=0,058) were higher in patients with grade 2 diarrhea. The relationship between side effects and genetic mutations was analyzed using chi-square test. No statistically significant differences between genotypes and the most frequently observed side effects of diarrhea (*p*=1.00) and mucositis (*p*=0.490) were observed.

Homozygosity for the *ABCC11* (rs17822931) variant (*A*) was not observed in the studied population, and thus the pharmacokinetic parameters were evaluated based on the dominant model. The mean 5-FU $AUC_{0\text{-}96h}$ values and heterozygous and mutant allele carries distributions are shown in Table 4. No statistically significant differences between 5-FU $AUC_{0\text{-}96h}$ values and *ABCC5* (rs562; *T>C*) and *ABCC11 (*rs17822931; *G>A*) gene mutations were observed in this cohort (Table 4, Fig. 2A, Fig. 2B).

Table 4. *Statistical analysis for the relationship between genotypes and 5-FU $AUC_{0\text{-}96h}$ levels.*

Genotype		n	AUC (mg.h/L)	SE	*p* value
ABCC5	*T/C: C/C*	16	21.04	3.46	
(rs562)					0.261
	T/T	2	16.65	0.0	
ABCC11	*G/A:A/A*	4	17.08	4.39	
(rs17822931)					0.564
	G/G	14	21.54	3.79	

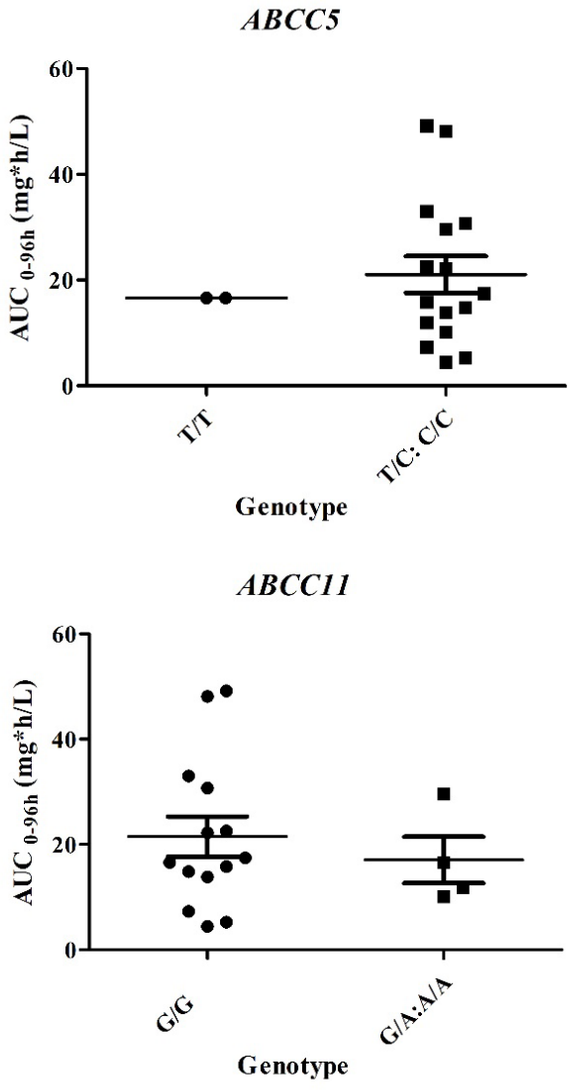

Fig 2. *Box plot showing AUC_{0-96h} values of each subject individually for variants of (A) ABCC5 (rs562, T>C) and (B) ABCC11 (rs17822931, G>A).*

4. DISCUSSION

The aim of this study was to examine whether specific SNPs in genes encoding *ABCC5* (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) affect the pharmacokinetics of 5-FU in patients with advanced gastric or gastro-esophageal junction cancer. This is the first study to examine the effect of these SNPs in *ABCC5* and *ABCC11* on exposure of 5-FU regimens in advanced gastric cancer patient. The blood samples for pharmacokinetics analysis were collected on day 1 of the first cycle, 24 hr after 5-FU administration which indicates the C_{ss} of 5-FU. Because of the short half-life of 5-FU (10–15 minutes), the C_{ss} of the samples are suggested to be taken at least 18 hr after the start of 5-FU infusion (9,10). 5-FU infusion started at the same time for all patient and plasma samples were collected near the same time of the day after starting infusion to eliminate circadian changes in 5-FU metabolism (19–21).

The AUC levels of this study showed high inter-patient 5-FU AUC_{0-96h} variability, which is consistent with previous reports showing more than 40% coefficient of variation (CV). There were no significant correlations between BSA and 5-FU exposure in this study. According to therapeutic window of 5-FU infusion (AUC 20-30 mg.h/L), 23% of patients had an AUC within the therapeutic range, 16% of patients were overdosed, and 61% were underdosed. Our results are in the same range as previous studies reporting that 20-30% of patients were treated in the appropriate dose range, approximately 40-60% of patients were underdosed, and 10-20% of patients were overdosed (8–10).

We observed a nearly two-fold higher AUC_{0-96h} levels in patients with mucositis (n=5; mean AUC_{0-96h}: 28.37±19.53 mg.h/L) and diarrhea (n=3; mean AUC_{0-96h}: 33.22±15.86 mg.h/L) versus patients without these toxicities. The mean 5-FU AUC_{0-96h} values were around the toxicity levels (AUC>30 mg.h/L) according to previous studies (9). There was no statistically significant correlation likely due to the small sample size.

No statistically significant differences were seen between 5-FU AUC_{0-96h} values and *ABCC5* (rs562, *T>C*) and *ABCC11* (rs17822931, *G>A*) gene mutations in this cohort. Importantly, this is the first study to examine the effect of these SNPs in *ABCC5* and *ABCC11* on pharmacokinetics of 5-FU. This is related to findings with different outcomes of previous studies even if one cannot directly compare the current findings with former reports. The *ABCC5* (rs562, *T>C*) heterozygous patients (*T/C:C/C*) had slightly higher mean 5-FU AUC_{0-96h} levels versus wild type patients (*T/T*): 21.04 ±3.46 µg.h/ml and 16.65 µg.h/ml, respectively. However, the statistical analysis showed no significant differences in our findings (p=0.261). This is in contrast to the results of Teft et al. (2015) who noted significantly reduced irinotecan and metabolite (SN-38G and APC) levels in *ABCC5* (rs562) '*C*' allele carriers (*CC* and *TC* genotypes) versus wild type (*TT*) patients (22). On the other hand, Lal et al. (2017) found no significant impact of *ABCC5* (rs562, *T>C*) polymorphism on doxorubicin pharmacokinetic parameters (23).

The *ABCC11* (rs17822931, *G>A*) heterozygous patients (*G/A : A/A*) had a mean 5-FU AUC_{0-96h} of 17.04 ±4.39 mg.h/L, which was slightly lower than *G/G* carriers 21.54 ±3.79 mg.h/L. In addition, due to previous findings about rs17822921, we expected an alteration in 5-FU AUC_{0-96h} levels. Particularly lower 5-FU AUC_{0-96h} values were expected in patients carrying the mutant type because the mutant form of *ABCC11* lacks an N-linked glycosylation (24,25).

Dose limiting toxicities of 5-FU include diarrhea, abdominal pain, nausea, stomatitis, mucositis, and hand-foot syndrome (26,27). At the end of the first cycle, the most frequently observed side effects were diarrhea and mucositis (related to 5-FU); however, we did not note any hand-foot syndrome or stomatitis. No statistically significant differences between genotypes and the most frequently reported side effects were observed.

5. CONCLUSION

There was no significant impact of *ABCC5* (rs562; *T>C*) and *ABCC11* (rs17822931; *G>A*) found on the pharmacokinetics of 5-FU. Therefore, we recommend studying these SNPs in *ABCC5* and *ABCC11* more precisely in a larger cohort. This could be an important determinant for 5-FU-based treatment sensitivity and might contribute to personalized therapy for patients receiving 5-FU.

Conflict of Interest: The authors declare that they have no conflict of interest.

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