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Fixed dose capecitabine is feasible: results from a pharmacokinetic and pharmacogenetic study in metastatic breast cancer

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Abstract

Purpose—The pro-drug capecitabine is approved for treatment of anthracycline- and paclitaxel-resistant metastatic breast cancer. However, toxicity and large interpatient pharmacokinetic variability occur despite body surface area (BSA)-dosing. We hypothesized that a fixed-dose schedule would simplify dosing and provide an effective and safe alternative to BSA-based dosing.

Patients and Methods—We conducted an open label, single-arm, two-stage study of oral capecitabine with fixed starting dose (3,000 mg total daily dose in two divided doses × 14days q21days) in patients with metastatic breast cancer. We correlated pharmacodynamic endpoints (e.g., efficacy [response] per RECIST and toxicity), adherence and pharmacokinetics/pharmacogenetics. Sample size of 45 patients was required to detect a 25% response rate from null response rate of 10% using a Simon two-stage design.

Results—Twenty six patients were enrolled in the first-stage and 21 were evaluable after a median of 4 cycles of capecitabine. Two thirds of patients received either the same dose or a dose 500 mg lower than what would have been administered with a commonly used 2,000 mg/m^2 BSA-dosing schedule. Eight patients had stable disease but progressed after a median of 7 cycles. Despite a clinical benefit rate of 19%, no RECIST responses were observed following the first stage and the study was closed. Dose-reductions were required for grade 2 hand-foot syndrome (28%) and vomiting (5%). Adherence was similar when using both patient-reported and Medication Event Monitoring System (MEMS) methods. High interpatient variability was

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observed for capecitabine and metabolite pharmacokinetics, but was not attributed to observed pharmacogenetic or BSA differences.

Conclusion—Single agent activity of capecitabine was modest in our patients with estrogen receptor-positive or -negative metastatic breast cancer and comparable to recent studies. BSA was not the main source of pharmacokinetic variability. Fixed-dose capecitabine is feasible, and simplifies dosing.

Keywords

breast cancer; capecitabine; pharmacokinetics; pharmacogenetics

Introduction

Capecitabine is an oral fluoropyrimidine pro-drug that is approved for the treatment of anthracycline- or taxane-resistant metastatic breast cancer alone or in combination with docetaxel at a dose of 2500 mg/m^2 (total daily dose) orally given in two divided daily doses for 14 days followed by 7 days of rest [11]. In the initial studies that led to approval of capecitabine by the U.S. Food and Drug Administration (FDA), the overall response rate was 25.6% as monotherapy [6] and 42% when combined with docetaxel [22]. However, clinical experience with this drug has led to the observation that significant gastrointestinal and dermatologic toxicity occurs at high frequency, as well as wide interpatient pharmacokinetic variability, when the recommended dose is administered to patients [16, 24]. This has led to the investigation and clinical use of lower doses than the approved dose, which appears to be associated with acceptable efficacy and reduced toxicity [3, 8, 25].

Body surface area (BSA) based dosing is the most frequently used method of calculating drug dose for chemotherapeutic agents. Traditionally, this approach was thought to reduce variability of interpatient drug exposure and therefore drug effects. However, it has been shown that BSA-based approach still results in large interpatient variability in drug exposure. In a retrospective analysis of 33 investigational agents tested in phase 1 clinical trials, BSA-based dosing was not associated with a reduction in interpatient variability in drug clearance for capecitabine [4]. These results suggest that dosing strategies other than BSA should be evaluated when developing new anti-cancer agents. Alternative dosing schedules for capecitabine (e.g., “7-day on/7-day off”) using a fixed schedule have indeed previously been investigated, but have not reported pharmacokinetic or pharmacogenetic endpoints to date [10, 32].

We hypothesized that a flat-fixed-dose schedule would simplify dosing and provide an effective and safe alternative to BSA-based dosing. We therefore conducted a phase II trial in patients with metastatic breast cancer to explore the efficacy and safety of flat-dose capecitabine at 3,000 mg (total daily dose) given in two divided daily doses for 14 days, repeated every 21 days. The dose was selected based on the commonly used dose (2000 mg/m^2 with rounding down to nearest 500 mg multiple) for a woman with a BSA of 1.7 m^2. We also evaluated adherence to capecitabine, pharmacokinetic variability associated with the flat-dose, pharmacogenetic contribution to pharmacokinetic variability, and correlation of pharmacokinetics and pharmacogenetics with toxicity and efficacy.

Patients and Methods

Study Oversight

The study was designed by the senior academic authors. Data were collected by the Johns Hopkins Breast Cancer Program data management team and analyzed by Dr. Garrett-Mayer as the lead statistician. The academic first, second, and last authors of this article prepared

the manuscript draft. All coauthors made additional contributions to the interpretation of the data and subsequent editing. The pharmaceutical sponsor reviewed the manuscript prior to submission but was not involved in its writing.

Eligibility

Women (≥ 18 years or older) with a histologically confirmed metastatic (stage 4) adenocarcinoma of the breast were eligible. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; measurable disease; adequate hematologic, hepatic and renal function; and up to three prior cytotoxic regimens for metastatic disease. Prior therapy with capecitabine was not allowed.

Patients were excluded if they had another active malignancy, serious concurrent medical conditions, pregnancy, or untreated brain metastases unless small volume and approved by the principal investigator. Those with an active gastrointestinal malabsorption illness; prior unanticipated severe reaction to fluoropyrimidine therapy; known hypersensitivity to 5-FU or known dihydropyrimidine dehydrogenase (DPD) deficiency were also excluded. Concomitant use of CYP2C9 substrates (i.e., warfarin or phenytoin) was not permitted. The clinical protocol was approved by the Johns Hopkins Institutional Review Board and all subjects provided written informed consent prior to study drug administration.

Drug Dosage and Administration

Capecitabine was provided as 500 mg tablets by Roche Laboratories, Inc. It was stored and handled per standard instructions for the commercially available product [11]. Patients were advised to take the medication within 30 minutes after the ingestion of food and swallow with approximately 200 mL of water.

The starting dose of capecitabine was 3,000 mg (total daily dose) given in two divided daily doses for 14 days followed by 7 days of rest (1 cycle = 21 days). Missed doses were not substituted. The drug vials were fitted with a Medication Event Monitoring System (MEMS VI; AARDEX Group Ltd., Sion, Switzerland) cap for the duration of study therapy to collect data on medication adherence. Patients also documented drug administration with a study drug diary. Pill counts were performed by the study team. Dose modification was preferred over the concomitant use of colony-stimulating factors. Treatment was continued until unacceptable toxicity, disease progression, or withdrawal of consent.

Dose Modification

Toxicity was assessed using the National Cancer Institute/Division of Cancer Treatment Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3. Excessive toxicity was defined as capecitabine-related grade 4 neutropenia ≥ 5 days in duration, grade 4 thrombocytopenia of any duration, or any grade 3–4 non-hematologic toxicity.

Up to three dose reductions below the initial cycle 1 dose were permitted (one fewer 500 mg tablet per day per cycle). Dose re-escalation could be considered if the subject tolerated the reduced dose for at least one cycle. Instructions were provided for the management of treatment-related diarrhea, nausea/vomiting and hand-foot syndrome. Up to two dose escalations were permitted after the first two cycles (one additional 500 mg tablet per day each cycle) if no excessive toxicity was observed in a previous cycle.

Pretreatment and Follow Up Studies

Baseline evaluations included routine history and physical examination, complete blood counts, serum chemistries and radiologic evaluations. Clinical evaluations and laboratory tests were repeated monthly for the first two cycles and then every two cycles thereafter.

Response of measurable lesions was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) after every 4 cycles [7]. Patients were followed for toxicity assessment for 30 days after going off-study.

Pharmacokinetic Sampling and Analysis

Capecitabine pharmacokinetic samples were collected pre-treatment and post-treatment at 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 8 hours. Trough levels were evaluated by obtaining samples within 30 min prior to the dose administration on days 2, 8 and 15 of cycle 1 with optional weekly samples for the duration of the study. Tetrahydrouridine, a cytidine deaminase inhibitor, was added at a final concentration of 400 nM to increase the stability of capecitabine and metabolites in plasma during storage in the freezer [5, 26, 35]. Capecitabine and metabolites (5′DFCR, 5′-DFUR, and 5-FU) concentrations were measured using a validated analytical assay consisting of high-performance liquid chromatography with tandem mass spectrometric detection over the range of 50 ng/mL to 10,000 ng/mL [35]. Pharmacokinetic parameters were calculated by standard noncompartmental methods using WinNonlin professional (version 5.3) as previously described [1, 14]. The effect of BSA on the pharmacokinetic parameters of capecitabine was assessed as previously described [4].

Adherence Studies

Patients completed a pill diary noting the date and time that each dose was taken, including any dose modification and reason. In addition, the MEMS was utilized to collect data on medication adherence. If the MEMS cap was removed, it was presumed that the patient took the medication within 30 minutes. Adherence was calculated utilizing both methods based on the number of doses administered per total number of doses per cycle (n=28).

Pharmacogenomic Studies

The three-step enzymatic process of pro-drug activation from capecitabine to 5-fluoro-5′-deoxycytodine (5′DFCR) and then 5-fluoro-5′-dexoxyuridines (5′-DFUR) has been well described. Thymidine phosphorylase (TP) as the final enzyme involved in the conversion to 5-FU is tumor specific and selectively upregulated by capecitabine, [28] while 5-FU is inactivated by dihydropyrimidine dehydrogenase (DPYD) [12]. Due to the small sample size, genetic associations with pharmacodynamic markers (e.g., thymidylate synthase) were not assessed. The relationship between pharmacokinetic parameters and genetic variants involved in drug disposition of capecitabine (e.g., carboxylesterase (CES) [17], cytidine deaminase (CDA) [9], dihydropyrimidine dehydrogenase (DPYD) [2], and the solute carrier SLC28A1 [18]) were explored [24]. Genomic DNA was isolated using the Gentra Puregene kit (Gentra Systems, Inc., Minneapolis, MN) following the manufacturers' instructions. Samples were genotyped using Pyrosequencing assays for CDA K27Q (rs2072671), CES2 -830 (rs11075646), DPYD*2A (rs3918290), DYPD*5 (rs1801159), and SLC28A1 V189I (rs2290272) as previously described [2, 9, 17]. Primers for the CES2 and SLC28A1 SNPs were designed using PyroMark Assay Design Software 2.0. The PCR primers for CES2 -830 were AGTTTATTGCCCCCTCCTATCGA (forward-biotinylated) and GGGAATCCTCTCTTCAAACCTGTCC (reverse, annealing temperature 60°C) and were GGCCCCACAACTAGCACTCACT (forward-biotinylated) and GTGGGGGTGCAATGCTGA (reverse, annealing temperature 62°C) for SLC28A1 V189I. The internal sequencing primers were CGATGAGCGCGCTGG and CAGGAATCTGCGTGT, for CES2 and SLC28A1, respectively and the sequences to analyze were GGSATCGATAGGAGGGGGCAATAAACTA and TCRTCGCTCTCCTCTTTGCCTGCTCAAA, respectively.

Statistical Analysis

For the purposes of the primary endpoint of response rate, a two-stage design was used. If two or fewer responses were seen in the first 22 evaluable patients (first stage), the study was to be suspended. If three or more responses were seen in the first stage, enrollment would continue to approximately 45 evaluable patients (second stage). This design provided 80% power with 5% type I error (two-sided) to detect a response rate of 25% from a null rate of 10%. Differences in adherence were compared between patient-reported and MEMS methods using a Wilcoxon signed rank test. Patients who were adherent and for which complete pharmacokinetic sampling were collected were considered evaluable for pharmacokinetic analysis and were included in the descriptive statistics. Allele frequencies were calculated by allele counting and deviations from Hardy-Weinberg equilibrium were assessed using ^{2} tests. The Fisher's exact test was used to determine the association between pharmacokinetic parameters, tumor response and genetic variants. All *P*-values were two-sided, not adjusted for multiple comparisons, and were considered significant at a $P<0.05$.

Results

Patient Characteristics

Thirty patients with metastatic breast cancer were consented between August 2005 and December 2008. Twenty six patients were eligible and initiated treatment on-study and patient characteristics are summarized in Table 1. A total of 115 cycles of therapy were administered and five patients did not complete cycle 1. The median number of cycles initiated was 4 (range 1–16).

Dose modifications

All patients received the pre-defined starting dose of capecitabine of 3,000 mg orally daily given in two divided doses. Two thirds of the patients received either the same dose or a 500 mg lower dose compared to what would have been administered with a commonly used BSA dosing schedule (2000 mg/m^2 with rounding down to nearest 500 mg multiple). There was no correlation between BSA and those patients who had their dose escalated or reduced ($P>0.05$). In the case of two patients, dose escalation of capecitabine to 3,500 mg total daily dose was performed after cycles 3 and 5 of therapy. For the former patient, dose reduction to 3,000 mg was required after cycle 5 due to the development of grade 2 hand-foot syndrome. Dose reductions are described below with safety data.

Efficacy

Twenty-one patients were evaluable for response. Five did not complete cycle 1; three patients developed progressive disease during cycle 1, one patient developed a right atrial thrombosis and congestive heart failure after four days of therapy and one patient had an ongoing wound infection that pre-dated study entry. No responses by RECIST criteria were seen (response rate 0%). Nine patients had stable disease after two cycles. Clinical benefit rate, defined as complete response plus partial response plus stable disease (SD) ≥24weeks, was 19% (four patients with SD ≥ 24 weeks). Twelve patients had progressive disease as best response and stopped study therapy after a median of 4 cycles (range 2–4). Median time to treatment failure was 12 weeks (range 6–48) and the median number of cycles was 7 (range 2–16).

Safety and Tolerability

Potentially treatment-related toxicities of all grades and for all cycles are listed in Table 2. No unexpected capecitabine-related toxicities were observed. Grade 3 drug-related toxicities were infrequent and included fatigue (n=1) and hand-foot syndrome (HFS) (n=2). The most

frequent non-hematological adverse events were HFS (77%), fatigue (61%), nausea (54%), mucositis (27%), diarrhea (27%) and vomiting (23%). Doses were reduced to 2,500 mg in 6 patients due to grade 2 HFS. Three of these patients reduced dose a second time, to 2,000 mg, for recurrent grade 2 HFS and 1 of these 3 reduced a third time to 1,500 mg for grade 3 HFS. One patient reduced dose in cycle 1 due to grade 2 vomiting. Among the 2 patients whose dose was escalated to 3,500 mg daily, both only received the higher dose for 1 cycle. One patient was later dose-reduced to 3,000 mg daily for grade 2 HFS while the other had progressive disease.

Adherence

Utilizing the patient-reported method, 46% (12 of 26) of patients did not report missing any capecitabine doses although a time of dose administration was not always recorded. Of those that reported missed doses, 14% (2 of 14) reported missing five or fewer doses, 46% (7 of 14) reported missing six to 14 doses, 1% (1 of 14) reported missing 19 doses, and 29% (4 of 14) did not document dosing times. According to the MEMS method of documentation, 50% (13 of 26) of patients did not miss any capecitabine doses. Of those patients with documented missing doses with the MEMS method, 23% (3 of 13) missed five or fewer doses, 46% (6 of 13) missed six to 14 doses, and 31% (4 of 13) did not turn in the MEMS device to calculate this information. Two of the 4 patients who did not participate in the patient-reported method also did not turn in the MEMS device. However, in assessing overall adherence, both methods yielded similar results per patient ($P > 0.05$).

Capecitabine Pharmacokinetics

Summary plasma pharmacokinetic parameters of capecitabine and its metabolites for 26 patients are listed in Table 3. High interpatient variability was observed for capecitabine and metabolite pharmacokinetic parameters but was similar to previous findings [30]. The interpatient variability in the apparent oral clearance of capecitabine (42.5% vs. 45.4%) was similar after correction for BSA. There was no correlation observed between pharmacokinetic parameters and toxicity ($P > 0.05$).

Pharmacogenomics

We assessed the association of capecitabine and metabolite pharmacokinetics with common germline variants in carboxylesterase, cytidine deaminase, dihydropyrimidine dehydrogenase, and the solute carrier SLC28A1 (see Table 4). All genotype frequencies were in Hardy–Weinberg equilibrium. No patient with a mutant allele in DPYD*2A was identified, which was expected on the basis of earlier frequency data. There was no correlation between standard pharmacokinetic parameters and the genetic variation in carboxylesterase, cytidine deaminase, dihydropyrimidine dehydrogenase, and the solute carrier SLC28A1 ($P > 0.05$; only data for AUC is presented in Table 4). In addition, there was no correlation between the genetic variation and toxicity ($P > 0.05$; data not shown). This study was limited by the small sample size and the relatively low genetic variability.

Discussion

Capecitabine is used widely as a therapeutic strategy in patients with metastatic breast cancer in the first-line setting and beyond based on a relatively favorable safety profile and substantial anti-tumor activity. However, in clinical practice, the FDA recommended dose (2,500 mg/m^2 given in two divided daily doses for 14 days followed by 7 days of rest) [11] is often not well tolerated due to diarrhea, nausea/emesis and hand-foot syndrome. Leonard et al suggest that dose reductions can be as high as 41% when capecitabine is administered alone and 65% when combined with docetaxel [15]. Therefore, a starting dose of 2,000 mg/m^2 is now commonly used in clinical practice and in recent clinical trials [31] with similar

apparent efficacy. However, the persistent use of BSA-based dosing despite evidence against its using it for many drugs in clinical practice continues despite the lack of scientific support. [4, 19, 23, 27].

Our primary hypothesis was that the standard BSA-based capecitabine regimen could be simplified by the use of a fixed-dose regimen, providing an effective and safe alternative. While our study did not meet the pre-defined primary endpoint of response rate and was closed after the first stage of accrual, the overall clinical benefit rate (lack of progression for at least 24 weeks) was 19% in a patient group that included ~60% with estrogen receptor-positive endocrine-resistant disease. Overall, the regimen was well tolerated with no observed adverse events greater than grade 3, and patients were generally adherent using self-reporting and electronic compliance monitoring methods.

Despite the low response rate observed, we confirmed that fixed-dose capecitabine is feasible, and simplifies dosing. Equally important, we also confirmed that the high interpatient variability observed for capecitabine and metabolite pharmacokinetics is not attributed to observed pharmacogenetic or BSA differences. The observed anti-tumor activity in our study, although far lower than the initial studies that led to regulatory approval of single agent capecitabine [6], is potentially comparable to more recent studies in the metastatic setting [33]. For example, a flat-dose capecitabine schedule (7 days on, 7 days off) starting at 1,500 mg orally twice daily with maximum tolerated dose found to be 2,000 mg twice daily give to 21 patients with a similar disease phenotype (~ 60% ER-positive) in the first line setting resulted in one partial response and a 28% clinical benefit rate [33]. While it is possible that the lower starting dose in our study might have resulted in a lower clinical activity when compared to usual BSA-based dosing of 2,000 mg/m2 daily, we think this is unlikely as a third of our patients ultimately required dose reduction due to excessive toxicity.

A potential explanation for the variable response rate observed with capecitabine between clinical trials may relate to differences in the patient population enrolled. The XCALIBr study reported an overall response rate of 38% for the combination of capecitabine plus bevacizumab in a human epidermal growth factor-2 (HER2)-negative metastatic breast cancer population with a response rate of 47% in the ER-positive population and 27% in the ER-negative population [29]. Similar findings favoring ER-positive disease were observed in a preplanned exploratory analysis of adjuvant capecitabine in combination with docetaxel, cyclophosphamide and epirubicin, [13] although patients with ER-negative disease appeared to benefit more from the addition of adjuvant capecitabine to standard chemotherapy in another randomized phase 3 adjuvant trial [21]. Overall, robust predictors of response to capecitabine and the reasons for variation in patient outcomes between clinical trials remain elusive.

The capecitabine pharmacokinetic profile observed in our study was highly variable between patients but was similar to previous findings [30]. Others have assessed the influence of BSA on drug clearance when utilizing BSA-based dosing. Since we performed the analysis utilizing a flat-dose, we were able to confirm previous findings that indeed BSA differences did not add to the observed pharmacokinetic variability [4]. In addition, the pharmacokinetic variability was not associated with pharmacogenetic variability in the enzymes involved in capecitabine’s disposition. Finally, the mild toxicities observed did not correlate with pharmacokinetic or pharmacogenetic variability, but these pre-planned analyses are limited by the small sample size and do not rule out potential contribution by rare functional variants.

In summary, despite the absence of a response reported in our study, a small clinical benefit rate of 19% was observed. Flat fixed-dose capecitabine is feasible and tolerable; it simplifies dosing, and may reduce errors. Despite overall limited activity in the adjuvant setting, [20, 34] capecitabine remains an important therapeutic strategy in breast cancer due to its oral formulation, ease of dose modifications and administration in patients with liver dysfunction, and the lack of cumulative toxicity following long periods of administration. Future studies may wish to compare standard versus alternative capecitabine schedules if robust biomarkers of response to therapy or predictors of toxicity are identified, which is the subject of an ongoing study being conducted by the Translational Breast Cancer Research Consortium (NCT00977119).

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Table 1

Baseline patient characteristics

Characteristics	Number of patients (n=26)
Age, years	
Median	53
Range	32–73
BSA, m^2	
Median	1.89
Range	1.63–2.21
Race	
Caucasian	16
Black	9
Other	1
ECOG Performance status	
0	16
1	10
Disease status	
Locally advanced	0
Metastatic	26
Location of disease	
Visceral	3
Non-visceral	4
Both	19
ER/PR-positive/ HER2-neg	12
HER2-pos	3
ER-pos	2
ER-neg	1
Triple-negative (ER,PR,HER-2 negative)	11
No. of patients treated with prior chemotherapy for metastatic disease	7
Number of prior chemotherapy regimens for metastatic disease	
1	2
2	4
Median no. of regimens for metastatic disease (range)	0 (0–2)

Abbreviations: ER, estrogen receptor, PR, progesterone receptor, ECOG, Eastern Co-operative Oncology Group

Table 2

Treatment-related side effects occurring in > 1 patient

		N=26		
Toxicity	**Total Events**	**G1**	**G2**	**G3**
Anemia	3	2	1	
Fatigue	16	11	4	1
Anorexia	5	3	2	
Nausea	14	12	2	
Vomiting	6	3	3	
Diarrhea	7	6	1	
Constipation	2	2		
Dyspepsia	6	6		
Taste alteration	2	1	1	
Mucositis	6	1	7	
Pain-Abdomen NOS	4	2	2	
Hand-foot reaction	20	9	9	2
Rash	2	1		
Headache	5	4	1	
Sensory neuropathy	3	2	1	

Note: Number of worst grade adverse events possibly, probably, or definitely attributed to capecitabine during study drug administration. Toxicities are graded per the NCI CTCAE version 3 criteria. G1=Grade 1, G2=Grade 2, G3=Grade 3. NOS= not otherwise specified.

Table 3

Capecitabine pharmacokinetics compared to historical control [30]

	Current Trial (1500 mg BID)*	Historical Control [30] (1000 mg/m^2 BID)*
Capecitabine		
C_{max} (ng/mL)	9324±7015 (75%)	5651±5360 (95%)
AUC_{∞} (ng*h/mL)	7255±4180 (58%)	6810±3904 (57%)
5′-DFCR		
C_{max} (ng/mL)	6353±2590 (41%)	4578±2090 (46%)
AUC_{∞} (ng*h/mL)	11344±5583 (49%)	10299±3663 (36%)
5′-DFUR		
C_{max} (ng/mL)	4597±2608 (57%)	4906±2928 (60%)
AUC_{∞} (ng*h/mL)	6653±2166 (33%)	10519±3533 (34%)
5-FU		
C_{max} (ng/mL)	753±1209 (160%)	211±130 (61%)
AUC_{∞} (ng*h/mL)	1230±1826 (152%)	434±161 (37%)

*Data is presented as the mean ± SD (%C.V.)

AUC_{∞} area under the concentration–time curve from time zero to infinity, BID twice a day, C_{max} maximum plasma concentration, SD standard deviation

Table 4

Association of capecitabine pharmacokinetics and genetic variation*

		Allele frequency[1]				
Variant genotypes	**Count (Total)**	***p***	***q***	**Pharmacokinetic parameter**	***P***	**rs ID**
CDA K27Q (GG vs. GT vs. TT)	16/9/1 (26)	0.79	0.21	Capecitabine AUC_{∞}	0.24	rs2072671
				5′-DFCR AUC_{∞}	0.16	
				5′-DFUR AUC_{∞}	0.28	
				5-FU AUC_{∞}	0.19	
CES2 -830 (GG vs. GC vs. CC)	1/4/20 (25)	0.12	0.88	Capecitabine AUC_{∞}	0.94	rs11075646
				5′-DFCR AUC_{∞}	0.63	
				5′-DFUR AUC_{∞}	0.54	
				5-FU AUC_{∞}	0.10	
DPYD *2A (GG vs. GA vs. AA)	26/0/0 (26)	1.00	0.00	Capecitabine AUC_{∞}	n.a.	rs3918290
				5′-DFCR AUC_{∞}	n.a.	
				5′-DFUR AUC_{∞}	n.a.	
				5-FU AUC_{∞}	n.a.	
DPYD *5 (GG vs. GA vs. AA)	12/13/1 (26)	0.71	0.29	Capecitabine AUC_{∞}	0.78	rs1801159
				5′-DFCR AUC_{∞}	0.95	
				5′-DFUR AUC_{∞}	0.47	
				5-FU AUC_{∞}	0.20	
SLC28A1 V1891 (GG vs. GT vs. TT)	10/14/2 (26)	0.65	0.35	Capecitabine AUC_{∞}	0.33	rs2290272
				5′-DFCR AUC_{∞}	0.99	
				5′-DFUR AUC_{∞}	0.34	
				5-FU AUC_{∞}	0.10	

*Statistical associations were evaluated using the Fisher's exact test.

[1]Hardy-Weinberg notation for allele frequencies; p, frequency for reference allele and q, frequency for variant allele

Abbreviations: Cytidine deaminase (CDA), carboxylesterase 2 (CES2), dihydropyrimidine dehydrogenase (DPYD), n.a., not applicable.