Capecitabine-induced adverse events: a pharmacogenetic study beyond *DPYD*

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INTRODUCTION

- About 25-75% of patients treated with capecitabine develop hand-foot syndrome (HFS)[1]
- HFS can limit activities of daily living and can seriously impact patients quality of life[2]
- Occurrence of HFS during capecitabine often results in treatment interruptions (26%) or treatment discontinuations (17%)[1]
- Screening for DPD deficiency by testing for common single nucleotide polymorphisms (SNPs) in *DPYD*, the gene encoding DPD, followed by a dose reduction significantly reduced the incidence of fluoropyrimidine-related toxicity[3]
- However, the overall incidence of HFS is still high in patients treated with capecitabine

PRIMARY OBJECTIVE

To investigate whether SNPs in genes encoding for capecitabine metabolizing enzymes (*CES1*, *CES2,* and *CDA)* can be used to predict the occurrence of HFS in patients treated with capecitabine.

METHODS

- 446 patients treated with capecitabine at the Erasmus MC Cancer Institute were included for analysis
- Prospectively collected blood samples were genotyped for 8 SNPs in 3 genes:
  - *CES1* 1165-33 C>A (rs2244613)
  - *CES1* 1165-41 C>T (rs2244614)
  - *CES1* 690+129delC (rs3217164)
  - *CES2* 1613-108G>A (rs2241409)
  - *CES2* -823C>G (rs11075646)
  - *CDA* -79A>C (rs2072671)
  - *CDA* -205C>G (rs603412)
  - *CDA* 266+242A>G (rs10916825)
- HFS was graded according to the Common Terminology Criteria for Adverse Events version 5.0
- Associations between SNPs or baseline factors (age, sex, performance status) and HFS with $P \leq 0.10$ were tested multivariably by logistic regression and internally validated by bootstrapping

RESULTS

Baseline patients' characteristics

Characteristics	Total study cohort N = 446 patients	Patients with HFS (all grades) n=146
Sex (%)		
Male	249 (55.8)	72 (49.3)
Age (years, median, [IQR])	62 [54-69]	60 [52-69]
ECOG performance status (%)		
1	302 (67.7)	1 (0.7)
2	10 (2.2)	0
3	1 (0.2)	0
BSA (median, [IQR])	1.92 [1.77-2.06]	1.89 [1.68-2.06]
Primary tumor type (%)		
Colorectal	295 (66.1)	95 (65.1)
Esophagus/Gastric	80 (17.9)	18 (12.3)
Breast	53 (11.9)	27 (18.5)
Neuro-endocrine [A]	8 (1.8)	2 (1.4)
Other [B]	10 (2.2)	5 (3.4)
Metastatic disease (%)	182 (40.8)	72 (49.3)
Treatment regimen		
Capecitabine monotherapy	80 (17.9)	40 (27.4)
Capecitabine + radiotherapy	96 (21.5)	20 (13.7)
Capecitabine + oxaliplatin	170 (38.1)	50 (34.2)
Capecitabine + bevacizumab	16 (3.6)	12 (8.2)
Capecitabine + epirubicin + oxaliplatin	15 (3.4)	3 (2.1)
Capecitabine + epirubicin + cisplatin	52 (11.7)	13 (8.9)
Capecitabine + temozolomide	7 (1.6)	2 (1.4)
Other [C]	10 (2.2)	6 (4.1)
Capecitabine cumulative daily dose (%)		
≥ 4000 mg	86 (19.3)	41 (28.0)
3500 mg	217 (48.7)	74 (50.7)
≤ 3000 mg	143 (32.0)	31 (21.2)
Capecitabine adjustment/discontinuation (%)		
Due to adverse events	126 (28.3)	59 (40.4)
Occurrence of hand-foot syndrome		
CTCAE grade 1	69 (15.5)	69 (47.3)
CTCAE grade 2	62 (13.9)	62 (42.5))
CTCAE grade 3	15 (3.4)	15 (10.3)

[A] Neuro-endocrine tumor: bronchus (n=5), jejunum (n=2), pancreas (n=1), and thymus (n=1)
[B] Other tumor types: appendix (n=2; n=2), duodenum (n=2; n=1)), goblet cell (n=1; n=0), jejunum (n=2; n=0), pancreas (n=1; n=0), papilla of Vater (n=1; n=1)), and pseudomyxoma peritonei (n=1; n=0).
[C] Other treatment regimen: capecitabine + trastuzumab (n=4; n=3), capecitabine + lapatinib (n=2; n=1), capecitabine + bevacizumab + paclitaxel (n=2; n=1), capecitabine + vinorelbine (n=1; n=0), and capecitabine + cisplatin + pembrolizumab (n=1; n=0).
Abbreviations: IQR: interquartile range; CTCAE: common terminology criteria for adverse events.

Investigated single nucleotide polymorphisms

Gene	SNP ID	Variant	MAF	No. of WT	No. of HET	No. of HVAR	HWE *P*-value
CES1	rs2244613	1165-33C>A	19%	298	130	18	0.42
CES1	rs2244614	1165-41C>T	58%	82	214	150	0.71
CES1	rs3217164	690+129delC	51%	111	217	117	0.60
CES2	rs2241409	1613-108G>A	18%	297	133	15	0.98
CES2	rs11075646	-823C>G	10%	361	81	4	0.82
CDA	rs2072671	-79A>C *2	35%	197	185	64	0.06
CDA	rs603412	-205C>G	42%	155	205	85	0.24
CDA	rs10916825	266+242A>G	35%	187	206	53	0.74

Abbreviations: MAF: minor allelic frequencies; WT: wild types; HET: heterozygous variants; HVAR: homozygous variants; HWE: Hardy-Weinberg equilibrium.

Associations of selected single nucleotide polymorphisms with HFS

Endpoint	Factor	Comparison	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	Bootstrap 95% CI	P
HFS All grades	Sex	Female vs. Male	1.479 (0.994-2.201)	0.053	1.385 (0.926-2.073)	(-0.081-0.728)	0.113
	CES2 -823C>G	GG + CG vs. CC	0.412 (0.230-0.739)	0.002	0.432 (0.240-0.777)	(-1.542- -0.278)	0.005
HFS ≥ grade 2	Sex	Female vs. Male	2.008 (1.220-3.305)	0.006	2.161 (1.293-3.610)	(1.293-3.610)	0.003
	CES1 690+129delC	-/- + C/- vs. CC	0.576 (0.338-0.980)	0.040	0.758 (0.415-1.384)	(0.415-1.384)	0.367
	CES1 1165-33C>A	AA + CA vs. CC	2.015 (1.222-3.321)	0.005	1.888 (1.075-3.315)	(1.075-3.315)	0.027
	CDA 266+242A>G	GG + AG vs. AA	1.747 (1.035-2.951)	0.035	1.865 (1.087-3.200)	(1.087-3.200)	0.024

Abbreviations: HFS: Hand-foot syndrome.

CONCLUSION AND FUTURE PERSPECTIVES

- Carriers of *CES1* 1165-33C>A and *CDA* 266+242A>G polymorphisms are at higher risk of developing HFS ≥ grade2 during capecitabine treatment. This is in line with previous research.[4]
- Prospective studies should investigate if preemptive screening for these SNPs can be used to individualize systemic cancer treatment.
- Additionally, *CES2* -823C>G was associated with a reduced risk on developing HFS. Replication of this association is needed.

References
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M. de With has no conflicts of interest