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CASE REPORT

A Pharmacogenomic Basis for Tolerance of 5-Fluorouracil Following Early, Severe Toxicity from Capecitabine in a CDA Ultrarapid Metabolizer Colon Cancer Patient: A Case Report

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Introduction: Capecitabine is an oral prodrug that is converted to 5-FU via three enzyme-catalysed steps: carboxylesterase (CES), cytidine deaminase (CDA), and thymidine phosphorylase (TYMS). Approximately 80–90% of 5-FU, whether from capecitabine or direct administration, is quickly inactivated by dihydropyrimidine dehydrogenase (DPD), encoded by DPYD. Preemptive testing for four pathogenic DPYD variants that reduce DPD activity is advised; however, currently, no evidence for CES, CDA, or TYMS has necessitated a similar recommendation despite polymorphisms in these genes potentially causing treatment toxicity. The current preemptive testing guidelines for 5-FU and capecitabine are similar.

Case Presentation: A 74-year-old black woman with a caecal adenocarcinoma diagnosis of $pT_{4b}G_1N_0M_0$ was prescribed adjuvant oxaliplatin and capecitabine post-hemicolectomy. On day 16 of the first cycle, she presented with severe gastrointestinal, myelosuppressive, hand and foot side effects and enterocolitis infection. She underwent a pharmacogenomic workup with whole-exome sequencing and was noted to be genetically DPD non-deficient (DPYD *1/*9A). She was found to express CDA rs3215400 (c.-33delC) and CDA rs1048977, both of which are associated with an increased risk of toxicity from capecitabine. CDA rs3215400 has been specifically described as an ultrametabolizer variant with an observation to increase enzyme activity by 3–7 fold and the occurrence of adverse drug events in capecitabine. After recovery and follow-up, she continued to receive 5-FU, leucovorin, and oxaliplatin therapy which she tolerated well and completed six months of therapy.

Conclusion: This case shows that the severe adverse effects of capecitabine therapy in a patient with a CDA ultrametabolizer profile can be successfully switched to 5-FU-based therapy at a normal dose and tolerate this alternative fluoropyrimidine.

Keywords: fluoropyrimidine, genetic polymorphisms, toxicity, precision medicine, gastrointestinal cancer

Introduction

Capecitabine and 5-fluorouracil (5-FU) are fluoropyrimidines belonging to a class of antimetabolites. Capecitabine is an oral pro-drug that undergoes a 3-step enzymatic biotransformation to (5-FU), a process catalysed by carboxylesterase, cytidine deaminase, and thymidine phosphorylase which are encoded by the CES1, CDA, and TYMS genes, respectively. Approximately 80–90% of 5-FU formed from capecitabine or directly administered is rapidly metabolised into an inactive form by dihydropyrimidine dehydrogenase (DPD) which is encoded by the *DPYD* gene, as shown in Figure 1.[1] For cancer patients receiving fluoropyrimidine-based chemotherapy, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends pre-emptive testing for four pathogenic DPYD variants associated with reduced or deficient DPD enzyme activity. No testing recommendation currently exists for CES1, CDA, and TYMS before commencing capecitabine.[2–4] These four variants include DPYD*2A, DPYD *13, c.2846A>T and Hap B3 DPYD

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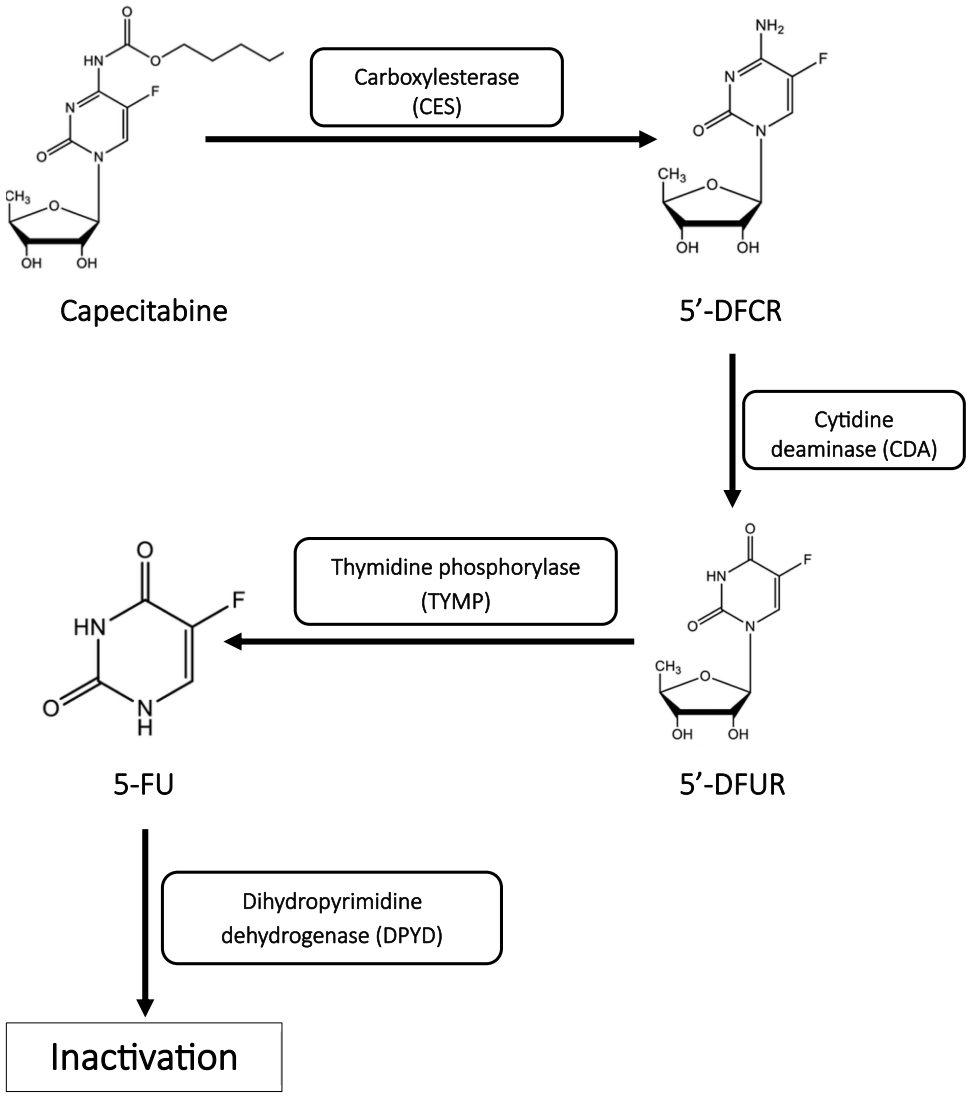

Figure 1 Fluoropyrimidine chemical structure and metabolic pathway showing capecitabine 3-step biotransformation via the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR), 5'-fluoro-5'-deoxyuridine (5'-DFUR) and ultimately to 5-Fluorouracil (5-FU). 5-FU is inactivated via the action of Dihydropyrimidine dehydrogenase (DPYD).

variants.[5] Treating patients based on these genotype results reduces the risk of fluoropyrimidine toxicity, helping to reduce treatment interruption and even the risk of death. The recommendations for 5-fluorouracil and capecitabine were similar. Among Caucasians approximately 5–7% of the population are DPD-deficient due to one of these four variants and pre-emptive DPYD testing improves patients' outcomes. Studies among Black Africans in Zimbabwe have previously shown that these four DPYD variants are rarely expressed in African populations, despite an equally high risk of adverse events compared to other ethnicities.[6] Africa has the highest genetic diversity worldwide.[7–9]

In this case report, we present a patient with cancer who commenced standard-dose capecitabine-based chemotherapy and experienced severe early adverse effects (AE). A pharmacogenomic workup showed her to be DPD non-deficient but noted her to have a CDA variant that confers an ultrametabolizer functional status. After recovery from AE, the patient was treated with 5-FU based chemotherapy and tolerated a normal dose well, completing the cycles without interruptions. This case shows that 5-FU can be considered in patients who experience adverse effects of capecitabine who are DPD non-deficient and are noted to be ultrametabolizers in the capecitabine biotransformation cascade. These patients can still benefit from fluoropyrimidine therapy, and pharmacogenomic testing for CDA should be investigated to

determine whether fluoropyrimidine pharmacogenomic guidance needs to discriminate between the two medicines. A CARE checklist was used to write the report.

Case Report/Case Presentation

A 74-year-old black Zimbabwean woman with pre-existing type 2 diabetes mellitus and hypertension was diagnosed with caecal adenocarcinoma following colonoscopy after presenting with weight loss, loss of appetite, and generalised body weakness. The patient had no known drug allergies, no prior history of cancer diagnosis, sober habits, non-smoking status, retired status, and diabetes mellitus and hypertension were well-controlled. She had no known family history of chronic diseases. A disease staging Contrast-enhanced CT tomography of the chest, abdomen, and pelvis revealed no distant metastases. Right hemicolectomy and primary anastomosis were performed, and the histology was reported to be $pT_{4b}G_1N_0M_0$. The postoperative recovery was uneventful. According to the disease stage and high-risk status, a multidisciplinary team recommended that she receives 8 cycles of adjuvant oxaliplatin + capecitabine (oxaliplatin 130 mg/m^2 on day 1, capecitabine 1000 mg/m^2 twice daily for 14 days, every 21 days).

All baseline haematological, renal, and hepatic function tests were normal when adjuvant treatment was commenced at the full dose. On day 16 of the initial treatment cycle, the patient presented to the emergency room at midnight with complaints of abdominal pain, diarrhoea, vomiting, asthenia, and skin swelling, discoloration and peeling off of the hands and feet. These symptoms were identified as severe adverse drug reactions based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5). Clinical evaluation, including history, physical examination, and laboratory investigations, revealed grade 3 oral mucositis, anorexia, abdominal pain, diarrhoea, dehydration, hand-foot syndrome, and grade 4 enterocolitis. Additionally, the patient had grade 2 vomiting, and hypokalaemia, and grade 1 anaemia and neutropenia. She was admitted to the hospital for acute stabilisation and care, fluid resuscitation, potassium supplementation, loperamide administration, antibiotic therapy, and cardiac and blood sugar monitoring. Her recovery was initially slow; however, after about a week of supportive care, her condition improved, and she was eventually discharged after nine days. The care received during this admission period alone amounted to a minimum of US $ 3660.00.

After discharge, she was prescribed a topical urea cream for hand and foot syndrome and continued to recover to full health at home with regular follow-up visits. She was referred to a pharmacogenomics consultation clinic, where open-array multigene panel genotyping was initially performed. Genotyping showed that she had none of the four pathogenic DPYD variants, that is, she was genetically non-deficient for DPD according to the CPIC guidelines. Whole exome sequencing was then performed, and it confirmed she was DPD non-deficient genetically having DPYD*1/*9A. A review of the genes coding for the enzymatic biotransformation of capecitabine to 5-FU (CES1, CDA, and TYMS) showed that the patient expressed CDA rs3215400 (homozygous mutant 1/1) and CDA rs1048977 (heterozygous 0/1), whereas the rest of the cascade enzymes were normal (Table 1). These variants conferred a CDA ultrametabolizer (UM) phenotype in the patient based on previously reported clinical and pharmacokinetic studies.[10,11]

Sixty days after the presentation of severe AE, the patient restarted adjuvant chemotherapy with capecitabine and switched to 5-FU to bypass the capecitabine biotransformation pathway with the CDA UM profile. She received mFOLFOX6 (oxaliplatin 85 mg/m2 on day 1, leucovorin 400 mg.m2 on day 1, 5-FU 400 mg/m2 bolus on day 1, and 2400 mg/m2 infusion over 48 h – 2 weeks). She went on to complete six months of treatment, tolerating the treatment well, and no further severe AE or interruptions were recorded.

Method for Genetic Testing

Sample Collection and DNA Extraction

Whole blood (4mL) was collected from each participant into EDTA-coated tubes (BD Vacutainer®) to prevent coagulation. Genomic DNA was extracted from 200 µL of whole blood using a PureLink Genomic DNA Mini Kit (Invitrogen, Thermo Fisher Scientific) following the manufacturer's protocol. The DNA concentration was quantified using a Qubit® 4 Fluorometer (Thermo Fisher Scientific) with a Qubit dsDNA HS Assay Kit, ensuring high sensitivity for low-

Table 1 Patient Whole Exome Sequencing Results for the Genes Involved in Capecitabine Biotransformation Showing Presence of CDA rs3215400 and rs1048977 Variants

Gene Symbol	Chrom	Polymorphism ID	Zygosity	Consequence
DPYD	chr1	rs1760217	Heterozygous (0/1)	*1 Intron variant
		rs1801265	Homozygous mutant (1/1)	*9A Missense (Cys→Arg)
CES1	chr16	rs7187684	Homozygous mutant (1/1)	Intron variant and non-coding transcript-variant
CES2	chr16	rs11863141	Heterozygous (0/1)	Synonymous variant
TYMS	chr18	rs2853741	Homozygous mutant (1/1)	Upstream gene variant
	chr18	rs45445694	Heterozygous (0/1)	Upstream gene variant
	chr18	rs1360196663	Heterozygous (0/2)	Upstream gene variant
	chr18	rs699517	Heterozygous (0/1)	Downstream gene variant
	chr18	rs11280056	Heterozygous (0/1)	Downstream gene variant
CDA	chr1	rs3215400	Homozygous mutant (1/1)	5'UTR variant, non-coding exon variant, regulatory variant
	chr1	rs1048977	Heterozygous (0/1)	Synonymous variant

Note: *Star Allele.

concentration samples. To assess DNA integrity and purity, an Agilent TapeStation 4150 (Agilent Technologies) was employed, with DNA Integrity Numbers (DIN) ≥8.0 considered optimal for downstream sequencing applications.

Whole Exome Sequencing (WES)

WES was conducted to profile the coding regions of the genome comprehensively. Library preparation was performed using the Illumina® DNA Prep with the Exome 2.5 Enrichment Kit, which includes enzymatic fragmentation, end repair, adapter ligation, and PCR amplification. Exome capture was performed using the Illumina Exome Panel, targeting >99% of the coding regions (CCDS) with high specificity. Sequencing was performed on an Illumina NextSeq 2000 platform using a P3 2×150 bp paired-end flow cell, generating ≥50x mean coverage depth across the exome. Base calling and real-time analysis were conducted using Illumina DRAGEN Onboard (v4.4) to ensure high-quality raw data output.

Bioinformatics Analysis in Brief

Data Preprocessing

Raw sequencing data (BCL files) were demultiplexed using bcl2fastq (v2.20) and converted to the FASTQ format. Quality control was performed using FastQC (v0.11.9) to assess read quality, identify adapter contamination, and determine GC content.

Alignment and Variant Calling

Reads were aligned to the GRCh38/hg38 human reference genome using DRAGEN (v4.4, Illumina). The DRAGEN pipeline incorporates key steps for robust variant detection, including BWA-MEM alignment, duplicate marking (picard-based), Base Quality Score Recalibration (BQSR) and GATK HaplotypeCaller for SNV/indel detection.

Variant Annotation and Prioritization

Identified variants were annotated using Ensembl VEP (v113). Annotation leveraged comprehensive databases including gnomAD (v3.1.2) for population frequencies, ClinVar for clinical significance, and PharmGKB for pharmacogenomic relevance. A custom Python script was developed to extract and filter variants specifically within the key pharmacogenes (*DPYD, TYMS, CDA, CES1/2*). This script focused on variants with known functional impacts (eg missense, loss-of-

function, and regulatory variants) and those relevant to ACMG/CPIC guidelines for clinical interpretation and drug-gene interactions (eg 5-fluorouracil toxicity risk variants in *DPYD*).

Genotype–Phenotype Reporting

To generate a clinically actionable report, variant call files (VCFs) were uploaded to the Bio.logis® Genomic Information Management System (GIMS). The platform integrates several features to facilitate comprehensive pharmacogenomic interpretation, including automated phenotype prediction; integration of CPIC, DPWG, and FDA PGx guidelines; and risk stratification for drug responses. The final reports were reviewed by a board-certified clinical pharmacogenomic specialist to ensure the accuracy and clinical relevance of interpretations.

Discussion

In this case, the patient initially received a standard dose of capecitabine and experienced early severe adverse effects that were life threatening and costly, especially in this limited resource setting. After recovery, the patient's care was guided by the WES pharmacogenomic results, with the decision to maintain fluoropyrimidine-based treatment by bypassing capecitabine enzymatic biotransformation. We theorised that capecitabine therapy would have severe AE, but a normal toxicity risk would be expected for 5-FU due to the CDA UM phenotype profile. Subsequent 5-FU treatment was severely AE free. In this case, even if the CPIC-recommended pre-emptive DPYD test for fluoropyrimidines had been performed, her genetic non-DPD-deficient status would have been reported, and no reason to alter the initial treatment plan was needed. CDA genotyping is not recommended in patients receiving capecitabine therapy. The discovery of the CDA genotype and the resultant UM phenotype allowed her to benefit from an alternative fluoropyrimidine drug and not an alternative class of drugs. The observed severe toxicity of capecitabine may be directly related to the increased 5-FU exposure resulting from CDA UM in non-DPD-deficient individuals.

As shown in Table 1, the patient carried the DPYD haplotype *1/*9A, with an activity score of 2, implying normal DPD activity.[5,12] It is important to note that in the literature, differing conclusions have been drawn regarding the association between the DPYD*9A genotype and fluoropyrimidine-related severe adverse events. Some studies have reported that DPYD*9A carriers experience an increased risk of severe gastrointestinal, myelosuppressive, and/or hand and foot syndrome adverse events.[13–16] Other studies on 5-FU pharmacokinetics and DPD phenotyping have also shown this phenomenon. However, the majority of studies on DPYD*9A have reported normal activity, and the current consensus is that DPYD*9A has normal activity, and no change in drug dose is required.[17,18] In this case, the subsequent tolerance to the normal dose 5-FU treatment is consistent with the current clinical consensus.

In our view, the significance of this case lies in the finding and use of CDA rs3215400 (c.-33delC, also known as c-943 insC) and rs1048977. The gene encodes cytidine deaminase which metabolises the second step of capecitabine metabolism, that is, conversion of 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR) (Figure 1). CDA rs1048977 has been associated clinically with sAE, such as hyperbilirubinemia, in a cohort study of 301 patients with colorectal cancer receiving capecitabine-based therapy, with an OR of 8.621 (95% CI: 1.058–70.247; p = 0.044) compared to normal metabolisers.[19] Additionally, CDA rs1048977 in a cohort of 161 was significantly associated with capecitabine toxicity and eventual treatment suspension secondary to toxicity with an OR = 2.17 (95% CI = 1.07–4.19, p = 0.032).[10]

CDA rs3215400 variants have been objectively observed to confer a cytidine deaminase UM phenotype, which results in above-average enzyme activity. Based on in silico analysis that has been published, the presence of a C allele in the CDA gene is thought to be critical for the reduced translation of CDA in a process mediated by E2F transcription factor binding. In CDA rs3215400 carriers, deletion of this C allele results in increased CDA gene expression, and the levels of cellular CDA mRNA are 3–7 fold above normal.[11] Two reports in the literature reported that CDA rs3215400 carriers experienced severe adverse effects, with a fatality rate of one and treatment discontinuation in the other. Furthermore, in both cases, researchers conducted a CDA phenotyping assay and observed CDA activity to be 180% and 193% higher than that observed in the general population.[20,21] Based on these observations, it can also be argued that a reduced dose of capecitabine could lower the risk of AE without necessarily compromising cancer control outcomes; however, further insight into this is needed. In this case, we opted to pursue 5-FU based chemotherapy at the normal dose. Clearly from this case, it can be reasonably considered that CDA genetic testing or CDA activity phenotyping

before fluoropyrimidine treatment could be a "separator test" used to assess if a patient's risk of AE is higher with capecitabine a pro-drug versus direct 5-FU treatment due to polymorphism in the biotransformation pathway. In these two case reports and our current case, the hypothesis for the observed early severe adverse events is that in a non-deficient DPD individual, increased cytidine deaminase activity results in increased 5-FU exposure, leading to severe toxicity.

This case once again underscores the importance of WES in pharmacogenomic implementation, which allows for better management of rare cases and allows accumulated sequencing and clinical data to be more readily available for hypothesis generation and testing.[22] Our case is whoever limited in that no pharmacokinetic or CDA/DPD activity assays for phenotyping were performed, and there is always the possibility that chance influenced the occurrence of severe AE unrelated to the CDA genotype/phenotype. It is well known that the first cycles of fluoropyrimidine therapy have a higher risk of AE than subsequent cycles.[1] However, an important strength of the WES results and treatment toxicity classification after the fluoropyrimidine switch was performed. There is a paucity of information on CDA genotype/phenotype frequencies in African populations.

In conclusion, given the centrality of fluoropyrimidines in the treatment of various cancers, this case highlights the need for further genetic and phenotypic studies on the impact of CDA polymorphisms or lack thereof. The key implication of this case is that capecitabine toxicity cannot always be explained solely by DPYD status and that other enzymes in the drug's activation pathway-particularly CDA-may play a decisive role in severe early adverse reactions, highlighting the need to broaden current pharmacogenomic assessment strategies. The patient's ability to tolerate 5-FU despite life-threatening capecitabine toxicity underscores the importance of individualized fluoropyrimidine selection and suggests that CDA ultrarapid metabolizer phenotypes may guide safer treatment choices in similar clinical scenarios.

Data Sharing Statement

Anonymized data is available on request from the corresponding author.

Statement of Ethics

This case report was exempt from committee ethics approval; however, written informed consent was obtained from the subject of the case report, including consent for publication of the details of their medical case and the accompanying test results.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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