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SHORT COMMUNICATION

# Do 5-fluorouracil therapies alter CYP2C19 metaboliser status?

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**Abstract**
*Purpose* To report a case of altered CYP2C19 metaboliser status following 5-fluorouracil treatment.
*Methods* A 78-year-old male with stage III colorectal adenocarcinoma was prescribed with weekly iv 5-fluorouracil and folinic acid (FU/FA). Fourteen weeks after starting FU/FA, the patient was enrolled in a clinical study to investigate the role of tumour burden on drug metabolising enzyme activity. *CYP2C19* genotype was determined and the activity of CYP2C19 was measured using proguanil (PG) as a probe substrate. A metabolic ratio (PG/CG) for CYP2C19 activity was determined on three separate occasions, 7 days apart.
*Results* The patient was homozygous wild type (*CYP2C19*1/*1*), and on the first test, the metabolic ratio was concordant with the extensive metaboliser genotype. However, at day 14 and day 21, the metabolic capacity of this enzyme had decreased, and the subject had become a poor metaboliser (PG/CG > 30). The patient developed grade III hand and foot syndrome at day 10 of the study during the period of null CYP2C19 activity.
*Conclusions* Although 5FU is not a substrate for hepatic drug metabolising CYP enzymes, it may interfere with the synthesis of CYP2C19. Decreased activity of a related enzyme, CYP2C9, following 5FU has been reported previously. Down regulation of CYP2C9 and CYP2C19 synthesis by 5FU therapies may explain the adverse effect of 5FU on the clinical disposition of warfarin and phenytoin.

**Keywords** 5-Fluorouracil · CYP2C19 · Metaboliser status

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## Case report

The case was a male NZ European aged 78 (BMI 26.6) who was diagnosed with moderately differentiated adenocarcinoma of the sigmoid colon, stage T3N1. Following surgery, he was prescribed 5-fluorouracil 370 mg/m$^2$ (5FU) with folinic acid 20 mg/m$^2$ (FA) by weekly intravenous injection. The patient was recruited into a longitudinal study to investigate the role of tumour burden on the activity of CYP2C19. Ethical approval for this study was provided by the New Zealand Health and Disability Ethics Committee. At the time of inclusion into this study, serial whole body CT imaging had shown no evidence of metastatic disease.

Peripheral blood was used to genotype this patient for *CYP2C19* [1, 2]. The patient was homozygous wild type (*CYP2C19*1/*1*). This genotype predicts an extensive metaboliser (EM) status for drugs which are substrates for this enzyme [3]. The activity of CYP2C19 (phenotype) was determined on three separate occasions, each 7 days apart, using the probe drug proguanil [4, 5]. A proguanil metabolic ratio (PG/CG) was determined; individuals who are genotypic poor metabolisers have a PG/CG ratio of >10.

The phenotype at the first test was concordant with genotype, i.e. EM (PG/CG = 7.97). However, the two subsequent tests indicated that the metabolic function of this enzyme had dramatically decreased. No metabolite was detectable, indicating null metabolism (PG/CG > 30), and hence, the phenotype status was that of a poor metaboliser (PM).

This patient was in his 14th week of treatment. He ingested the probe drug at approximately midday and had a 2-h blood sample taken for measurement of proguanil metabolic ratio (PG/CG). He had received his most recent dose of 5FU/FA 7 days before phenotype testing. 5FU has a short half-life (~10–20 min) and does not directly inhibit CYP isozymes [6] and hence is unlikely to directly interfere with the metabolism of the probe drug.

## Discussion

5FU therapies are reported to interfere with the clinical disposition of warfarin and phenytoin [7–9]. These two drugs are substrates for CYP2C9 and to a lesser extent CYP2C19 [10, 11]. Limited evidence suggests that 5FU, although not a substrate for CYP enzymes, may alter CYP activity [6], such an effect may influence the disposition of these drugs.

It has been noted previously that 5FU can decrease the ability of a patient to metabolise the CYP2C9 probe drug, losartan, by up to threefold [12]. This previous report indicated that based on losartan metabolism this patient had "*substantially low activity of CYP2C9 compared to the population mean*" despite having a wild-type *CYP2C9*1/*1* genotype. Hence, 5FU may have the ability to decrease the activity of numerous CYP isozymes. Indeed chronic administration of 5FU is associated with down regulation of multiple CYP in rats [6]. One possible mechanism for this decreased activity could be down regulation of expression due to decreased rate of synthesis. Down regulation of CYP2C9 and CYP2C19 expression by 5FU may be a mechanism for the warfarin and phenytoin toxicity reported in patients receiving 5FU-containing therapies.

Patients with relatively low CYP2C19 activity prior to beginning 5FU may be at more risk of this delayed drug–drug interaction. Low baseline CYP2C19 activity would be expected in the 3% of Caucasians who are homozygous variant PM genotype [3]. However, we have recently noted that in advanced cancer patients with extensive metaboliser genotype, CYP2C19 activity is significantly compromised. Up to 37% of patients display a PM phenotype [13], and we hypothesise that these patients may be at increased risk of these drug–drug interactions.

The patient developed CTCAE grade III hand and foot syndrome at day 10 of participation in the study, during the period of null CYP2C19 activity (PG/CG > 30). Another patient in our study (NZ European female, aged 82) also developed this toxicity following treatment with capecitabine (schedule: 1,000 mg/m$^2$ b.d. for 21 days). This patient was also *CYP2C19*1*1* wild-type genotype and CYP2C19 activity was decreased at later timepoints (Day 1: PG/CG ratio = 6.72; day 30 = 14.3; day 56 = 9.1). Hand and foot toxicity developed 7 days after the last CYP2C19 phenotype test in this patient.

The causative mechanisms of hand–foot syndrome are poorly understood. However, it is intriguing to note that the symptoms are similar to those observed due to over exposure to vitamin A. We have demonstrated previously that a number of drugs associated with palmoplantar erythema can disrupt the ability of retinoic acid to control proliferation and differentiation of cells. These drugs include a number of substrates for the CYP2C isozymes. They can alter retinoid homeostasis via multiple mechanisms including direct inhibition of retinoic acid catabolism and displacement of retinoic acid from its binding protein (CRABP). This may result in inappropriately high levels of retinoic acid [14, 15]. 5FU down regulation of CYP involved in retinoic acid catabolism as a mechanism for the precipitation of hand and foot syndrome is a hypothesis that deserves further attention.

## Conclusion

Although 5FU is not a substrate for hepatic drug metabolising CYP enzymes, this antimetabolite may interfere with the synthesis of CYPs. A change in CYP2C19 activity status, from extensive to poor metaboliser, during 5FU treatment has not previously been reported. However, decreased activity of a related enzyme, CYP2C9, following 5FU treatment has been noted [12]. Since both CYP2C9 and CYP2C19 are important in the metabolism of warfarin and phenytoin, decreased synthesis of these CYP due to 5FU pre-treatment may explain the delayed drug–drug interaction observed between these agents and fluoropyrimidine drugs.

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