5-Fluorouracil/irinotecan induced lethal toxicity as a result of a combined pharmacogenetic syndrome: report of a case

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Dihydropyrimidine dehydrogenase (DPD, EC 1.3.1.2.) is the first and rate limiting enzyme of the pyrimidine catabolic pathway, with more than 80% of an administered dose of the chemotherapeutic drug 5-fluorouracil (5FU) being degraded by the enzyme, thus reducing its efficiency as a cytotoxic drug, and reducing drug toxicity due to accumulation of toxic metabolites. Following the initial description of familial pyrimidinemia and severe neurotoxicity after 5FU treatment, several reports appeared supporting the association between partial or complete DPD deficiency and severe 5FU induced toxicity, including lethal outcomes. Detailed investigations of the molecular genetics of DPD deficiency identified approximately 40 different genetic aberrations, including exon skipping, deletions, frameshifts, missense mutations, and polymorphisms.

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In white populations, it is generally accepted that a heterozygous 5′ splice site mutation in intron 14 (DPYD IVS14+1 G > A, designated DPYD*2A) occurs with a frequency of 1–2% in the general population. This mutation leads to exon 14 skipping and an altered protein, with reduced enzyme activity in heterozygotes and complete lack of catalytic activity in homozygotes.

The topoisomerase I inhibitor irinotecan displays potent activity against gastrointestinal malignancies and is being used in combined cancer chemotherapy approaches. The presence of reduced liver glucuronidation activity as a result of an aberrant UGT1A1 promoter (TA)n genotype, which underlies Gilbert’s syndrome, contributes to irinotecan toxicity.

We report a hitherto undescribed combined pharmacogenetic syndrome consisting of heterozygosity for DPYD*2A in the presence of a heterozygous UGT1A1 promoter (TA)n genotype underlying Gilbert’s syndrome causing lethal 5FU24h/folinic acid (FA)/irinotecan induced toxicity in a patient suffering from adenocarcinoma of the sigmoid colon.

CASE REPORT

A 44 year old white female index patient (BS) was diagnosed with a moderately differentiated adenocarcinoma of the sigmoid colon and underwent hemicolectomy and lymphadenectomy in 1995. As a result of liver metastases, hemihepatectomy was performed four years later. An exploratory laparotomy performed in January 2001 revealed advanced metastatic disease. Combined chemotherapy according to EORTC protocol 40986 was initiated and consisted of irinotecan (80 mg/m², 30 minute infusion), 5FU (2000 mg/m², 24 hour infusion), and FA (500 mg/m², two hour infusion) on a weekly basis. Nausea and vomiting (CTC grade 2), leucopenia (grade 1), and severe fatigue necessitated dose reduction after the second administration (irinotecan 64 mg/m², 5FU 1600 mg/m²). After dose reduction, no immediate nausea and vomiting were noted. However, the clinical condition deteriorated progressively to grade 4 toxicity (diarrhoea, neutropenia) and was further complicated by sepsis. Despite intensive medical care, the patient died from multiorgan failure.

DPYD*2A mutation genotyping by polymerase chain reaction mediated site directed mutagenesis followed by restriction fragment length polymorphism with the SnaBl restriction enzyme identified heterozygosity (fig 1), which was independently confirmed using a polymerase chain reaction restriction fragment length polymorphism assay with MaeII digestion. In addition, UGT1A1 promoter analysis was performed, and demonstrated a heterozygous UGT1A1 (TA)n genotype underlying Gilbert’s syndrome (fig 2).

DISCUSSION

Partial or complete deficiency of the rate limiting enzyme in pyrimidine catabolism, DPD, is increasingly being considered as a contributing factor to the occurrence and severity of 5FU toxicity. However, the overall impact of this pharmacogenetic syndrome on adverse drug reactions to treatment with fluoropyrimidine has not been established conclusively.

Abbreviations: DPD, dihydropyrimidine dehydrogenase; FA, folic acid; 5FU, 5-fluorouracil
Severe 5FU induced toxicity including a lethal outcome has been reported in several heterozygous DPD*2A mutation carriers. In addition, fatal fluoropyrimidine induced toxicity in patients with complete DPD deficiency and underlying homozygous DPD*2A mutation has been reported.\textsuperscript{7,8}14

Treatment for advanced colorectal cancer with 5FU/FA/irinotecan according to EORTC protocol 40986 in a 44 year old female patient who subsequently proved to be heterozygous for the DPD*2A mutation caused severe toxicity with a lethal outcome, thus supporting the concept that mutation carriers are at increased risk for fluoropyrimidine induced life threatening toxicity. However, several points need to be considered in the case presented here. First, a thorough phenotypic investigation was unfortunately not available for the patient. Therefore, the patient’s residual DPD enzyme activity remains speculative. Second, the index patient underwent combined palliative chemotherapy with 5FU/FA, and the topoisomerase I inhibitor irinotecan. Irinotecan itself has been implicated in a pharmacogenetic syndrome causing substantial drug induced toxicity.\textsuperscript{9} The prodrug irinotecan is bioactivated to the active compound SN-38, which in turn is the substrate for inactivating metabolic pathways consisting predominantly of glucuronide conjugation catalysed by liver microsomal uridine diphosphate glucuronosyltransferase, UGT1A1. Allelic (TA)\textsubscript{n} variants in the UGT1A1 promoter region, as seen in mild hereditary unconjugated hyperbilirubinaemia syndromes, are associated with reduced enzyme activity, which by impaired SN-38 conjugation could lead to toxicity. Indeed, severe irinotecan induced toxicity has been reported in two patients with metastatic colon cancer and hereditary unconjugated hyperbilirubinaemia or Gilbert’s syndrome.\textsuperscript{9} Pharmacogenetic analysis revealed that aberrant UGT1A1 promoter alleles represent a significant risk factor for severe irinotecan toxicity.\textsuperscript{10} Recent studies indicated that grade 4 neutropenia occurred much more frequently in patients with homozygous or heterozygous Gilbert’s syndrome than in wild-type carriers when irinotecan was administered as single drug treatment.\textsuperscript{11}

Figure 1

![Figure 1](http://jcp.bmj.com/first-published-as-10.1136/jcp.2004.022319-on-27-april-2005/downloaded-from)

**Figure 1** Polymerase chain reaction (PCR) mediated site directed mutagenesis followed by restriction fragment length polymorphism assay to detect DPDY IVS1-1 G > A (DPD*2A). After digesting the PCR product of 155 bp length with SnabI, two ethidium bromide stained bands of 155 and 131 bp length were seen for the patient (BS), indicating heterozygosity for DPDY*2A. Homozygosity for the wild-type DPDY allele with a single 131 bp band is shown for comparison (WT), in addition to a negative control (Neg) and a DNA ladder (L).

Take home messages

1. **We describe a patient who suffered severe gastrointestinal and haematological toxicity while undergoing combination 24 hour 5-fluorouracil/folic acid/irinotecan treatment for adenocarcinoma of the sigmoid colon, which led to her death**

2. **Molecular analysis revealed a novel combined pharmacogenetic syndrome, consisting of heterozygosity for the dihydropyrimidine dehydrogenase IVS1-1 G > A mutation and UGT1A1 (TA)\textsubscript{6/7} heterozygosity, which resulted in 5-fluorouracil/irinotecan intolerance and probably contributed to the fatal outcome**

3. **Combined pharmacogenetic approaches are required for adverse drug reactions associated with combined cancer chemotherapy**

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REFERENCES


