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

M Steiner, M Seule, B Steiner, I Bauer, M Freund, C H Köhne, P Schuff-Werner


CASE REPORT

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

M Steiner, M Seule, B Steiner, I Bauer, M Freund, C H Köhne, P Schuff-Werner


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, folinic acid; 5FU, 5-fluorouracil


www.jclinpath.com
Severe 5FU induced toxicity including a lethal outcome has been reported in several heterozygous DPYD*2A mutation carriers. In addition, fatal fluoropyrimidine induced toxicity in patients with complete DPD deficiency and underlying homozygous DPYD*2A mutation has been reported. Treatment for advanced colorectal cancer with 5FU24h/FA/Irinotecan according to EORTC protocol 40986 in a 44 year old female patient who subsequently proved to be heterozygous for the DPYD*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 5FU24h, FA, and the topoisomerase I inhibitor irinotecan. Irinotecan itself has been implicated in a pharmacogenetic syndrome causing substantial drug induced toxicity. 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)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. Pharmacogenetic analysis revealed that aberrant UGT1A1 promoter alleles represent a significant risk factor for severe irinotecan toxicity. 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.

‘The coexistence of more than one pharmacogenetic syndrome in a single patient seems possible’

Careful retrospective analysis of our index patient’s laboratory data revealed that pathological bilirubin concentrations were not noted, except slightly increased values immediately after abdominal surgery, which is not considered indicative of a hereditary unconjugated hyperbilirubinaemia. Nevertheless, UGT1A1 promoter analysis revealed the UGT1A1 (TA)6/7 genotype in our index patient. It has been estimated that (TA)6/7 heterozygotes have a 25% decrease in SN-38 glucuronidation activity, and either heterozygosity or homozygosity for the UGT1A1 (TA) allele confers a high risk (odds ratio, 7.2; 95% confidence interval 2.5 to 22.3) for severe irinotecan toxicity. Therefore, the aberrant UGT1A1 promoter genotype probably contributed to the severe toxicity seen in our index patient while undergoing combined treatment with 5FU24h/FA/Inotecan. This clearly illustrates that the coexistence of more than one pharmacogenetic syndrome in a single patient seems possible. Combined pharmacogenetic syndromes should be carefully investigated in patients with cancer showing severe toxicity while receiving several different chemotherapeutic agents.

Predictive pharmacogenetic testing is considered a potentially powerful approach to individualise cancer chemotherapy. With regard to fluoropyrimidine associated adverse drug reactions, currently available data are limited, rendering a recommendation for DPYD gene mutation(s) screening premature. In contrast, the association between Gilbert’s syndrome and irinotecan toxicity is firmly established, calling for pretherapeutic testing to reduce high grade toxicity.

In conclusion, the impact of a hitherto undescribed combined pharmacogenetic syndrome consisting of heterozygosity for DPYD*2A and UGT1A1 (TA)6/7 as related to 5FU24h/FA/irinotecan induced severe toxicity was demonstrated, thus calling for combined pharmacogenetic approaches to combined cancer chemotherapy associated adverse drug reactions.

**Take home messages**

- We describe a patient who suffered severe gastrointestinal and haematological toxicity while undergoing combination 24 hour 5-fluorouracil/folinic acid/irinotecan treatment for adenocarcinoma of the sigmoid colon, which led to her death
- Molecular analysis revealed a novel combined pharmacogenetic syndrome, consisting of heterozygosity for the dihydropyrimidine dehydrogenase IVS14+1 G > A mutation and UGT1A1 (TA)6/7 heterozygosity, which resulted in 5-fluorouracil/irinotecan intolerance and probably contributed to the fatal outcome
- Combined pharmacogenetic approaches are required for adverse drug reactions associated with combined cancer chemotherapy
REFERENCES


