Combined DPD and UGT1A1 Mutation in a Single Patient: A Case Report

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Abstract
Pharmacogenetic studies on 5-FU have mostly focused on enzyme Dihydropyrimidine Dehydrogenase (DPD), which is a rate-limiting enzyme in uracil and thymine catabolic pathway. Its activity has been found to be highly variable in different populations and several DPDY polymorphisms have been reported to be responsible for the decrease in activity of enzyme function and a high risk of 5-FU toxicity. Studies on 5-FU have mostly focused on t UGT1A1 genetic variations have been extensively investigated in relation to hyperbilirubinemia syndromes, as the UGT1A1 enzyme catalyses bilirubin glucuronidation. The importance of glucuronidation pathway in irinotecan treatment, UGT1A1 was chosen as the candidate gene to be investigated as a predictor of severe toxicity. Existence of combined mutation of DPD and UGT1A1 is adversely increases the treatment toxicity. A 57 year old male patient was diagnosed moderately differentiated adenocarcinoma rectum and patient was evaluated with DPD gene mutation found positive for Heterozygous (496A19), Homozygous (855/C) and Heterozygous (1627). Thereafter, the treatment regimen was changed to IROX, patient's conditions worsen progressively with Grade IV neutropenia and further complicated by sepsis. Patient was evaluated for UGT1A1 gene mutation. Subsequently, UGT1A1*1 and UGT1A1*28 gene was found to be mutated (Heterozygous).

Keywords: DPD; UGT1A1; 5FU; Irinotecan; Pharmacogenetics

Introduction
Fluorouracil (5-FU)-based therapy is employed in various oncology treatments such as GI, breast and aero-digestive tract cancer.

Fluorouracil (5-FU) therapy works by inhibition of thymidylate synthase and the metabolic impairment of DNA/RNA through its metabolite incorporation. The mechanism of action is influenced by the different modes of administration of 5-FU (infusion, bolus) [1,2].

Depending on the regimen of 5-FU therapy used some (10-30%) of patients also reported grade 3-4 toxicities with reported adverse effects such as myelosuppression, diarrhoea, mucositis and hand-foot syndrome [3].

A pharmacogenetics study of 5-FU metabolism depends on the rate-limiting catabolic enzyme, Dihydropyrimidine Dehydrogenase (DPD). DPD catabolizes some 85% of administered 5-FU with its impairments causes accumulation of 5-FU anabolics, thus causing toxicities in treated patients [4]. In general population frequency of DPD mutation is 1-2% [5].

Most of them adverse reactions of fluoropyrimidines are due to inter-individual genetic variations of DPD. Therefore its role in 5-FU therapies needs to be largely investigated. DPD activity is in fact highly variable in the population and its decreases enzyme activity and increased risk of 5-FU toxicity have been shown to be associated with several DPDY polymorphism. It is reported that 3-5% individual have been detected with DPD activities [6].

Irinotecan the semisynthetic derivative of camptothecin works by inhibition of ultracellular topoisomerase-1. This drug is metabolized by carboxylation into its active metabolite SN-38, which is in turn inactivated by uridine diphosphate glucorosyl transferase 1 (UGT1A1) into SN-38G and is excreted in the bile [7]. The most common irinotecan side effects are neutropenia, nausea, alopecia, febrile neutropenia and delayed diarrhoea. This main and dose limiting toxicity is due to β-glucuronidase in the bowel which reactivates SN-384 into its active metabolite SN-38 [8,9].

UGT1A1 genetic variations have been extensively investigated in relation to hyperbilirubinemia syndromes, as the UGT1A1 enzyme catalyses bilirubin glucuronidation.

There is a polymorphism in the promoter of UGT1A1 gene where seven instead of 6 TA repeats are found in the promoter region which causes most cases of this disorder. This polymorphism has been given the name UGT1A1*28 [10]. The importance of glucuronidation pathway in irinotecan treatment, UGT1A1 was chosen as the candidate gene to be investigated as a predictor of severe toxicity.

In the present study we report a case study of a patient suffering with adenocarcinoma of rectum where there is a combined pharmacogenetics syndrome that is homos with heterozygous for DPD gene (496A/G), (855/C) in the presence of the heterozygous gene UGT1A1.

Case Report
A 57 year old male patient from India was diagnosed moderately differentiated adenocarcinoma rectum with grade II in 2015. Patient underwent abdominal perianal resection followed by concurrent chemo radiation. The patient's treatment was started on Folfox-IV (Oxaliplatin, Leucovorin, 5FU) regimen, after 5-FU administration patient got Grade II diarrhoea & Grade II neutropenia after cycle 1 and Grade II diarrhoea with Grade III neutropenia after cycle 2 (CTCAE V4.0). Even after reducing dose of 5-FU, patient got diarrhoea and neutropenia. Patient was evaluated with DPD gene mutation and found positive

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for Heterozygous (496A19), Homozygous (855/C) and Heterozygous (1627) (Table 1). Thereafter, the treatment regimen was changed to IROX (Irinotecan and Oxaliplatin) regimen, after starting IROX regimen patient got Grade II diarrhoea and Grade II Neutropenia in 2 cycles. After dose reduction in next cycle, patient’s conditions worsen progressively with Grade IV neutropenia and further complicated by sepsis. After better ICU medical care patient came out from the sepsis. Keeping an account of IROX toxicity in mind, further patient was evaluated for UGT1A1 gene mutation. Subsequently, UGT1A1*1 and UGT1A1*28 gene was found to be mutated (Heterozygous) (Table 2).

Discussion

5FU is often the choice drug for colorectal cancer treatments. DPD activity is one of the main factors in determining drug exposure since 80% of the dose is metabolized by this enzyme in 5FU degradation [11]. PBMCs are often used as a surrogate for liver DPD activity as they are easily accessible [11] even though it is the liver which is primarily responsible for DPD activity for majority of 5-FU catabolism. The structural organization of DPD gene entails a 150 kb length with 23 exons ranging in size from 69-1404 bp [12]. Mutation in DPYD gene can be easily detected by the advent of rapid assays prior to the start of chemotherapy with 5FU. It is however important to identify those mutation that result in defective DPD protein. 19 molecular defects in the DPYD gene have been reported of late such as point/deletion due to exon skipping have been reported, but not all mutations results in DPD enzyme activity [12]. Lethal outcomes have also been reported in several heterozygous DPYD*2A mutation carries due to severe 5FU induced toxicity. In addition fatal 5FU induced toxicities have also been reported in patients with complete DPS deficiency having innate homozygous DPYD*2A mutations [5]. In an effort to identify relevant inherited variations to better predict patient response to chemotherapy new pharmacogenomics approaches have been initiated.

Functional changes in phenotype like changes in expression levels and/or activity of expressed proteins and their role in drug response has been extensively investigated in genetic polymorphisms of drug-metabolizing enzymes, transporters and molecular targets. The Uridine Diphosphate Glucuronosyltransferase (UDP-Glucuronosyltransferase or UGT) belong to a super family of enzymes which perform a reaction of conjugation. There are over 113 reported genetic variations of UGT1A1. UGT1A1*1 is denoted as the wild type allele and is linked to normal enzyme activity. Whereas, UGT1A1*28 is the most common variant allele and is found most frequently in African-Americans (0.42-0.45 allele frequency) and Caucasians (0.26-0.31), the most, and is less frequent in Asian populations (0.09-0.16) and these cases present a higher probability for irinotecan toxicity in blood [10,14,15].

In 2005, US FDA recommended that patients who are homozygous for UGT1A1*28 will have high risk by Irinotecan toxicity, and warn that patient should receive reduced starting doses.

Severe toxicity in a previous index patient who was DPD deficient could be attributed to the mutation in UGT1A1 promoter. Coexistence of both DPD and UGT1A1 mutation was reported in a single patient [11] till now as per literature search. This is one more rare case reporting of combined genetic syndrome and also for both mutation patient had heterozygous and homozygous association.

It is therefore essential that we advance our knowledge to first predict and then prevent the occurrence of toxicities related to 5FU. However, there is no consensus on screening of DPYD mutations prior to 5-FU treatment. Many DPYD allele variants have been discovered, but there has been a lack of consistency between the genetic variant and the degree of toxicity; many such individuals have toxicity profiles similar to those of the general population.

Whenever the patient has unexplained Neutropenia and Grade III & IV Gastrointestinal toxicity with standard dose of FOLFOX/IRINOTECAN, we should consider investigating the UGT1A1 mutation analysis.

Conclusion

Existence of combined mutation of DPD and UGT1A1 is adversely increases the treatment toxicity. Though simultaneous testing for the same is not recommended, one should consider the possibility of whether patient is intolerant to commonly used 5FU and Irinotecan based chemotherapy or not. Treatment efficacy of this combined pharmacogenetics syndrome is uncertain.

References


