Uracil-Dihydrouracil metabolism and *DPYD* polymorphisms as factors in the determination of 5-Fluorouracil-induced toxicity in Thai colorectal cancer patients

Chalirmporn Atasilp[1], Krish Danghorachai[1], Suthinan Chandawanich[1], Natchaya Vanwong[2], Phichai Chansriwong[3], Ekaphop Sirachainan[3], Thanyanan Reungwetwattana[3], Pimonpan Jinda[4] Somthawin Aiempradit[3], Suwannee Sirilerttrakul[3], Apichaya Puangpetch[4,5], THOMAS Fabienne[6,7], Chonlaphat Sukasem[4,5]

[1]Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand
[2]Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand
[3]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[4]Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[5]Laboratory for Pharmacogenomics, Clinical Pathology, Somdetch Phra Debharatana Medical Centre, Ramathibodi Hospital, Bangkok, Thailand
[6]Cancer Research Center of Toulouse, INSERM, UMR-1037, Paul Sabatier University, Toulouse, France.
[7]Laboratory of Pharmacology, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France.

Abstract

Background: Colorectal cancer is currently the 3rd most prevalent cancer in Thailand. The systemic medication for this disease has historically been a prescription involving 5-Fluorouracil (5-FU), an antimetabolite that may lead to serious toxicities. The occurrence of these side effects has been traced back to two main occurrences: *DPYD* polymorphisms as well as abnormal levels of Uracil (U) and Dihydrouracil (UH_2). Both of these factors indicate a compromise in the elimination of 5-FU via the Dihydropyrimidine Dehydrogenase (DPD) enzyme. Thus, an understanding of the two aforementioned factors in the context of each other can determine one's DPD efficiency, leading to individualized dosages that allow for the minimization of possible side effects. **Methods:** The *DPYD* polymorphisms were investigated to *DPYD IVS14 + 1G >A (*2A), 1896T>C, 85T>C, 1774C>T,* and *1627A>G (*5)* using Real-Time PCR. The U and UH_2 levels were determined by UPLC-MS/MS. The results showed that *DPYD*2A* and *1774C>T* were not prevalent within any of the 29 Thai colorectal cancer patients from Ramathibodi Hospital. **Results:** The *DPYD 1896T>C, 85T>C,* and **5* were prevalent within our sample. Although, there were no associated significantly between *DPYD* polymorphisms and U levels and UH_2 levels, the trends discovered were still of importance. The *DPYD 1896T>C* had data indicative of DPD deficiency in the context of DH_2 levels. The *DPYD 85T>C* and **5* had the pattern expected of DPD deficiency concerning the DH_2 levels and DH_2/U ratio. **Conclusion:** The presence of *DPYD 1896T>C, 85T>C*, **5* showed a trend of high U levels and DH_2/U ratios that could lead to side effects in Thai colorectal cancer patients. Thus, a large sample size would be required to confirm for further study.

Keywords: Uracil levels, Dihydrouracil levels, 5-Fluorouracil, Colorectal Cancer, Toxicity