A clinical pharmacogenetic characterization of DPD polymorphisms for pretreatment screening of patients candidates to fluoropyrimidine therapy

M. Del Re[1], F. Loupakis[2], C. Barbara[3], L. Lombardo[4], T. Latiano[5], E. Vasile[2], E. Zafarana[6], S. Cordio[7], L. Toffolatti[8], M. Ricasoli[9], A. Prestifilippo[10], F. Venturini[11], S. Di Donato[6], F. Grifalchi[12], A. Rinaldi[13], A. Butera[14], E. Maiello[5], S. Siena[11], A. Brandes[4], A. Falcone[2], F. Cappuzzo[3], R.Danesi[1]

[1]Dept of Clinical and Experimental Medicine, University of Pisa, Italy
[2]Medical Oncology Unit 2, Azienda Ospedaliero Universitaria Pisana, Italy
[3]Medical Oncology Unit, Ospedale Civile, Livorno, Italy
[4]Medical Oncology Unit, Bellaria Hospital, Bologna, Italy
[5]Medical Oncology IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
[6]Medical Oncology Unit, Ospedale Misericordia e Dolce, Prato, Italy
[7]Medical Oncology Unit - Garibaldi Hospital, Catania, Italy
[8]Medical Oncology Unit, Azienda Ospedaliera Vimercate, Monza, Italy
[9]Medical Oncology Unit, USL 3, Pistoia, Italy
[10]Medical Oncology Unit, Istituto Oncologico del Mediterraneo, Catania, Italy
[11]Medical Oncology Unit, Ospedale Niguarda Ca' Granda, Milano, Italy
[12]Medical Oncology Unit, Ospedale MG Vannini, Roma, Italy
[13]Medical Oncology Unit, Hospital Castellaneta, Italy
[14]Medical Oncology Unit, Hospital Agrigento, Italy

Background:DPD deficiency is an inherited syndrome resulting from loss-of-function mutations within the DPYD gene. The IVS14+1G>A variant is associated with DPD deficiency as a result of a 165-bp deletion in the DPD mRNA. A rare mutation, 2846A>T, is characterized by a change of the acidic aspartic acid to the aliphatic valine with potential impairment of enzyme activity (Amstutz et al., 2011). In this study, we describe the spectrum of toxicities of 5-FU and capecitabine in patients carrying the IVS14+1G>A and 2846A>T variants.**Methods:**Data were collected from 450 patients with gastrointestinal, breast and pancreas cancers. They were evaluated for DPD genotype upon development of grade ≥2 non-hematological and ≥3 hematological toxicities (CTCAE v. 4) secondary to standard fluoropyrimidine-containing regimens in combination with other cytotoxic agents and/or EGFR and VEGF antibodies. DNA was extracted from blood and IVS14+1G>A and 2846T>C DPD variants were screened on a Real-Time Life Sciences 7900 HT platform. The study was approved by the local Ethics Committee.**Results:**A total of 23 IVS14+1GA, five 2846AT, one IVS14+1AA and one 2846TT subjects were identified. Toxicities in all subjects were G3/4 diarrhea (100%), G3/4 mucositis (48%), febrile neutropenia (45%), G3/4 thrombocytopenia (38%), G3/4 anemia (24%), G2/3 hand-foot syndrome (14%), G3 dermatitis (7%) and G2/4 alopecia (7%). The homozygous patient was initially tested with a reduced 5-FU test dose and showed diarrhea grade 2, mucositis grade 3, anemia grade 1, pistrinopenia grade 3, febrile neutropenia grade 4, complete alopecia and Staphylococcus aureus sepsis. This patient required 20 days of hospitalization and was managed with antibiotics, platelet transfusion, port removal, G-CSF administration and parenteral nutrition. The IVS14+1AA patient survived because she was given a reduced 5-FU 250 mg/sqm test dose without folates, while the 2846TT patient deceased after the first cycle of FOLFOX4 treatment.**Conclusions:**Patients carrying the deleterious IVS14+1G>A and 2846T>C variant alleles display severe toxicities which is fatal in homozygous variant subjects. Although the frequence of DPYD*2A allele is low, the screening for DPD mutation is clinically relevant to avoid the severe toxicities or death in patients trated with fluoropyrimidine-containing regimens. This finding suggests the usefulness of pre-treatment screening of DPD in patients candidates to fluoropyrimidine treatment.

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Reference. Amstutz U, Froehlich TK, Largiadèr CR. Pharmacogenomics 2011;12:1321-36