Genetic Markers of Toxicity From Capecitabine and Other Fluorouracil-Based Regimens: Investigation in the QUASAR2 Study, Systematic Review, and Meta-Analysis

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Purpose Fluourouracil (FU) is a mainstay of chemotherapy, although toxicities are common. Genetic biomarkers have been used to predict these adverse events, but their utility is uncertain.

Patients and Methods We tested candidate polymorphisms identified from a systematic literature search for associations with capecitabine toxicity in 927 patients with colorectal cancer in the Quick and Simple and Reliable trial (QUASAR2). We then performed meta-analysis of QUASAR2 and 16 published studies (n = 4,855 patients) to examine the polymorphisms in various FU monotherapy and combination therapy regimens. Results Global capecitabine toxicity (grades 0/1/2 v grades 3/4/5) was associated with the rare, functional DPYD alleles 2846T>A and *2A (combined odds ratio, 5.51; P = .0013) and with the common TYMS polymorphisms 5’VNTR2R/3R and 3’UTR 6bp ins-del (combined odds ratio, 1.31; P = 9.4 × 10−6). There was weaker evidence that these polymorphisms predict toxicity from bolus and infusional FU monotherapy. No good evidence of association with toxicity was found for the remaining polymorphisms, including several currently included in predictive kits. No polymorphisms were associated with toxicity in combination regimens. Conclusion A panel of genetic biomarkers for capecitabine monotherapy toxicity would currently comprise only the four DPYD and TYMS variants above. We estimate this test could provide 26% sensitivity, 86% specificity, and 49% positive predictive value—better than most available commercial kits, but suboptimal for clinical use. The test panel might be extended to include additional, rare DPYD variants functionally equivalent to *2A and 2846A, though insufficient evidence supports its use in bolus, infusional, or combination FU. There remains a need to identify further markers of FU toxicity for all regimens.
[40] http://okina.univ-angers.fr/alain.morel/publications

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