Pharmacogenetics role of dihyropyrimidine dehydrogenase and thymidylate synthase genes in fluoropyrimidine-based chemotherapy.

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Abstract

Introduction & Aim: The fluoropyrimidine drug 5-fluorouracil (5-FU) and the prodrug capecitabine, have been extensively used for treatment of many types of cancer including colorectal, gastric and head and neck. Approximately 10% of the patients suffer from severe fluoropyrimidine-induced toxicity, like diarrhea, mucositis, myelosuppression and hand-foot syndrome. This may lead to dose reduction and treatment discontinuation. Pharmacogenetics research could be useful for identification of predictive markers in chemotherapy treatment.

Methods: Germline DNA was extracted from 83 cancer patients treated with fluoropyrimidine-based chemotherapy. In this study, we genotyped three polymorphisms in dihyropyrimidine dehydrogenase gene (rs3918290),(rs67376798),(rs55886062) and two polymorphisms, The variable number of tandem repeat (VNTR) polymorphism (rs45445694) and 6-bp insertion/deletion polymorphism(rs151264360) in thymidylate synthase gene. These genetic markers were correlated with toxicity to treatment. 5-FU-related toxicities such as Anemia, febrile neutropenia, neurotoxicity, vomiting, nausea and mucositis were evaluated according to NCI-CTC criteria version 4.0.

Results: DPYD gene polymorphisms was not observed in this study. The frequency of the TYMS +6 bp allele was 40.35% and the -6 bp allele was

59.65% in this study. And frequency of VNTR 2R allele was 48.75% and 3R allele was 51.15% .Toxicity grade two diarrhea, mucositis, nausea, vomiting and neurotoxicity are 2.2%,24.1%,15.7%,6% and 51.8%, respectively. Thymidylate synthase ins/del polymorphisms was significantly associated with increased grade three Neurotoxicity (p=0.02).

Conclusion: A pharmacogenetic approach could be a useful strategy for personalizing chemotherapy in cancer patients. Although rare DPYD polymorphisms was not observed in our study, according to large population studies, DPYD gene polymorphisms could be used as a predictive biomarker for efficacy of fluoropyrimidene-based chemotherapy .

Key words: Chemotherapy, Fluoropyrimidines, 5-fluorouracil, Colorectal cancer, Gastric cancer, Dihydropyrimidine dehydrogenase, Pharmacogenetics