Utility of Thymidylate Synthase Genotyping for 5-Fluorouracil Chemotherapy in a Large, Colorectal Cancer Cohort Study

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ABSTRACT

Introduction: 5-Fluorouracil (5-FU) chemotherapy in combination with leucovorin is the routine regime for advanced colorectal adenocarcinoma. 5-FU targets the enzyme, thymidylate synthase (TYMS), which provides the only de novo source of thymidylate for DNA synthesis. Germline polymorphisms in the 5'-promoter and 3'-untranslated region of the TYMS gene have been reported to modulate TYMS expression, responsiveness to 5-FU therapy, and clinical outcome. Our previous colorectal cancer outcome study of 150 Korean patients identified TYMS genotypes as the best prognostic indicator of 5-FU efficacy, evaluating 7 and 3 polymorphisms independently. The current study assesses these and an additional 5'-TSER polymorphism (G>C SNP) for independent and combined effects.

Methods: TYMS genotyping was assessed on 156 Korean colorectal surgery resected colorectal tumors from long-term follow up (mean overall survival 71 months, range 1-147, S.D. 50). One hundred and sixteen patients received chemotherapy and response and were controls for cancer stage, age, gender, and tumor location. The chemotherapy regimen consisted of 24 weeks of 5-FU at 425 mg/m2 , leucovorin at 20 mg/m2 , given on days 1, 5, every 4 weeks. The evaluated TYMS polymorphisms included a 6 base pair deletion of the 5'-UTR (DEL1) versus the wild-type insertion (INS). The number of patients with low and high expression genotypes were too limited to achieve statistical significance.

RESULTS: The TYMS genotype distributions for the 3'-UTR consisted of 10/156 (6.4%) patients with INS/INS (normal expression); 59/156 (37.8%) INS/DEL (intermediate expression); and 87/156 (55.8%) with high expression genotypes (11-2R/3RG, 54-3RG/3RC, 37-3RG/3RG). The chemotherapy regimen consisted of 24 weeks of 5-FU at 425 mg/m2 , leucovorin at 20 mg/m2 , given on days 1-5, every 4 weeks. The evaluated TYMS polymorphisms included a 6 base pair deletion of the 5'-UTR (DEL1) versus the wild-type insertion (INS). The number of patients with low and high expression genotypes were too limited to achieve statistical significance.

CONCLUSIONS: TYMS polymorphism genotyping may prove useful to stratify 5-FU chemotherapy response in colorectal cancer patients. Future studies are needed to evaluate the utility of 5-FU chemotherapy vs. other cytotoxic agents or in combination with chemotherapy.

INTRODUCTION

5-FU is commonly used for the routine treatment of many types of cancer including colorectal cancer. When 5-FU is administered, approximately 80 percent is catabolized by the dihydropyrimidine dehydrogenase (DPD2) into an inactive form and excreted in the urine.

The remaining drug is further metabolized into an active form that inhibits the synthesis of both DNA and RNA by either competitive inhibition of TYMS enzyme or by direct inactivation of cytokine metabolism into acid-soluble forms. The TYMS enzyme provides the only source of thymidine for de novo DNA synthesis. The drug is excreted in an inactive form and catabolized by the 5-FU dehydrogenase (DPD2) into an inactive form and excreted in the urine.

The results of this study are consistent with previous reports in other Asian populations. The number of TYMS T-UTR and 5'-TSER genotypes, categorized by cancer stage and expression, were too limited to achieve statistical significance.

REFERENCES