SHORT COMMUNICATION

Investigation of vascular invasion and genetic polymorphisms of DPD IVS14+1 G>A, UGT1A1 3156 G>A, and UGT1A1 28 tandem repeats in colorectal cancer patients in Taiwan

Ming-Yii Huang a,b,c,†, Meng-Lin Huang d,†, Jaw-Yuan Wang b,e,f,g,*, Shiu-Ru Lin h,i,**

a Department of Radiation Oncology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
b Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
c Department of Radiation Oncology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
d Division of Proctology, Department of Surgery, Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan
e Division of Gastrointestinal and General Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
f Department of Surgery, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
g Department of Medical Genetics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
h School of Medical and Health Sciences, Fooyin University, Kaohsiung, Taiwan
i Division of Medical Research, Fooyin University Hospital, Ping-Tung Hsien, Taiwan

Received 28 February 2012; accepted 26 March 2012
Available online 3 May 2012

KEYWORDS
colorectal cancer; DPD; genetic polymorphism; UGT1A1; vascular invasion

Abstract In the present study, multiple chemotherapeutic agent-related genetic polymorphisms, including dihydropyrimidine dehydrogenase (DPD) IVS14+1 G>A, UGT1A1 3156 G>A, and UDP-glucuronosyltransferase (UGT)1A1 28 tandem repeats, were analyzed in patients with colorectal cancer and studied in correlation with the clinical features of those patients. The genotypes from 273 patients with stages I–IV colorectal cancer who underwent operations were determined by means of polymerase chain reaction-restriction fragment length polymorphism. The results showed that the genotype distribution of DPD GG, UGT1A1 3156 GG, and UGT1A1 28 tandem repeats 5/6 or 6/6 in Taiwanese subjects were 98.4%, 82.2%, and 80.6%.

† Corresponding author. Division of Gastrointestinal and General Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, 100 Tzyou 1st Road, San-Ming District, Kaohsiung 807, Taiwan.
* Corresponding author. School of Medical and Health Sciences, Fooyin University, 151 Jinsyue Road, Daliao District, Kaohsiung 831, Taiwan.
** E-mail addresses: cy614112@ms14.hinet.net (J.-Y. Wang), srlin@ms2.hinet.net (S.-R. Lin).
† Ming-Yii Huang and Meng-Lin Huang contributed equally to this work.

2211-4254/$36 Copyright © 2012, Taiwan Genomic Medicine and Biomarker Society. Published by Elsevier Taiwan LLC. All rights reserved. doi:10.1016/j.gmbhs.2012.03.005
Introduction

Genetic polymorphisms in drug-metabolizing enzymes have been linked to interindividual differences in the toxicity and efficacy of medication.1 A pharmacogenetic approach may be an innovative strategy for optimizing chemotherapy in patients with advanced colorectal cancer. We analyzed several chemotherapeutic agent-related genetic polymorphisms, including dihydropyrimidine dehydrogenase (DPD) IVS14+1 G>A, UGT1A1 3156 G>A, and UDP-glucuronosyltransferase (UGT) 1A1 28 tandem repeats in Taiwanese colorectal cancer patients.2−6

Materials and methods

Consecutive 273 patients were prospectively enrolled in surgical units in Taiwan. Patients were required to have cytologically/histologically confirmed colorectal cancer disease. Blood samples were collected from these patients having stages I−IV colorectal cancer, and the DNA was isolated. A polymerase chain reaction-restriction fragment length polymorphism method was used to detect the frequency of the genotypes in our population. The associations of each genetic polymorphism with clinicopathological data of patients were further analyzed.

Results

Results showed that the genotype distribution of DPD GG, UGT1A1 3156 GG, and UGT1A1 28 tandem repeats 5/6 or 6/6 in Taiwanese subjects were 98.4%, 82.2%, and 80.6%, respectively. When analyzed jointly, a significant correlation was observed between vascular invasion and tumor invasion, lymph node metastasis, cancer stage, differentiation, perineural invasion, and survival (all $p < 0.05$). There was a statistical correlation between vascular invasion and tumor invasion, lymph node metastasis, cancer stage, differentiation, perineural invasion, and survival (all $p < 0.05$).

Discussion

DPD is a critical enzyme in the catabolism of 5-fluorouracil (5-FU), a drug frequently used in cancer therapy. One of the possible causes of severe 5-FU toxicity is genetic polymorphisms in the DPD gene, such as IVS14+1 G>A.2−6 Irinotecan unexpectedly causes severe toxicity of leukopenia or diarrhea. It is metabolized to form active SN-38, which is further conjugated and detoxified by UGT1A1 enzyme. Genetic polymorphisms of the UGT1A1 would affect an interindividual variation of the toxicity by irinotecan via the alternation of bioavailability of SN-38.2−6

The results of the present study highly suggest that DPD GG, UGT1A1 3156 GG, and UGT1A1 28 repeat 5/6 or 6/6 genotypes and vascular invasion could be prognostic factors for Taiwanese patients with colorectal cancer.

Acknowledgments

This study was supported by grants from the Kaohsiung Medical University Hospital (KMUH100-048), ZuoYing Armed Forces General Hospital (ZAFGH 100-05, ZAFGH 101-07) and by an Excellence for Cancer Research Center Grant (DOH101-TD-C-111-002) through funding by the Department of Health, Executive Yuan, Taiwan (ROC) and the Grant of Biosignature in Colorectal Cancers, Academia Sinica, Taiwan.

References