Study on the relationship among gene polymorphism, 5-FU plasma concentration and adverse reactions in the chemotherapy of colorectal cancer

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Background
5-FU is the first-line medicine for colorectal cancer chemotherapy. Gene polymorphism is a pivotal factor for predicting the adverse reactions of 5-FU. However, most studies focus on the relationship between the genetic polymorphism of a specific metabolic enzyme and the adverse reactions of 5-FU, which often cause conflicting conclusions. This study aims at detecting the polymorphisms of 5-FU metabolism enzymes, and blood concentration, as well as collecting the clinical toxicity data, and then performing the correlation analysis among them. This research will provide the basis for individualized treatment of 5-FU.

Methods
Detect the polymorphisms of 5-FU metabolic enzymes (DPYD and MTHFR) of the CRC patients treated with mFOLFOX6 using pyrosequencing. Blood samples were collected after 18-30h infusion of 5-FU after the second cycle to detect the serum concentration and calculate AUC value. WHO adverse reaction assessment method was used to evaluate toxicity.

Results
1. 57 CRC patients included 1 case of DPYD*2A heterozygous and homozygous mutation separately, 2 case of DPYD c.1679TG, 26 cases of MTHFR 677CT, 6 cases of MTHFR 677TT, 21 cases of MTHFR 1298AC, 5 cases of MTHFR 1298CC; the incidence of myelosuppression, vomiting, and diarrhea in patients with DPYD heterozygous mutation plus MTHFR mutation, and DPYD homozygous mutation was 100%.
2. The AUC of 5-FU was normally distributed in 57 CRC patients ranging from 4.9 to 38.4 mg·h /L, with the median level of 21.6 mg·h/L. There were 35 cases with AUC<22 mg·h/L, 14 cases with AUC 22-27 mg·h /L and 8 cases >27 mg·h/L. The incidence of grade III-IV toxicities in the 3 groups were 10.5%, 12.4% and 62.5%, respectively. 5-FU is effective and safe in the AUC range of 20-27 mg·h/L.
3. The AUCs of patients with DPYD heterozygous mutation plus MTHFR mutation, and DPYD homozygous mutation were >27mg·h /L.

Conclusions
DPYD heterozygous mutation plus MTHFR mutation, and DPYD homozygous mutation, can be used as predictive factors of 5-FU toxicity; there is no significant relationship between MTHFR polymorphisms and 5-
FU adverse reactions.