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ABSTRACTS

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Effects of Genetic Polymorphisms of Thymidylate Synthase (*TS*) and Methylenetetrahydrofolate Reductase (*MTHFR*) Along With Folate Intake on Clinical Outcome of Gastric Cancer Patients Treated With Fluorouracil-Based Chemotherapy

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Background: Several reports have evaluated treatment outcome of fluorouracil (FU)-treated gastric cancer patients based on genetic polymorphisms of *TS* (thymidylate synthase), a key target of FU, or *MTHFR* (methylenetetrahydrofolate reductase), a key enzyme of folate metabolism. However, the clinical data have been controversial. Furthermore, interaction between genetic polymorphisms of *TS* or *MTHFR* with folate intake is considered important in terms of gastric cancer risk. However, to our knowledge, there are no reports that evaluate simultaneously the effects of genetic polymorphisms and folate intake on clinical outcome of gastric cancer patients treated with FU-based chemotherapy.

Methods: We retrospectively analyzed the effects of genetic polymorphisms of *TS* and *MTHFR* on survival, and estimated folate intake by food frequency questionnaire, in 132 patients with advanced gastric cancer who were treated with first-line FU-based chemotherapy.

Results: Median overall survival (OS) was 11.3 months (95% CI, 9.4 – 13.4 months) and median progression-free survival (PFS) was 5.2 months (95% CI, 4.1 – 6.3 months). In a multivariate Cox model, patients with *TS*-3'UTR 6bp insertion, *MTHFR* 677 TT, and folate intake >260 µg/day had a better prognosis. Patients with at least one of two favorable genotypes (*TS*-3'UTR 6bp insertion and/or

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MTHFR 677 TT, n=33) had a significantly better survival compared with patients without any favorable genotypes (n=99; OS 18.8 vs. 10.2 months; HR 0.52; 95% CI, 0.33–0.80; $P = .004$), regardless of folate intake. Similar results were observed for PFS (HR 0.59; 95% CI, 0.38 – 0.92; $P = .02$).

Conclusion: These findings indicate that genetic polymorphisms of *TS* and *MTHFR* as well as folate intake have a substantial effect in FU-based chemotherapy in advanced gastric cancer. Further prospective evaluation is warranted.