

Impacts of fluorouracil-metabolizing enzymes on the outcomes of patients treated with S-1 alone or S-1 plus cisplatin for first-line treatment of advanced gastric cancer

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A phase III trial of S-1 plus cisplatin (SP) versus S-1 alone, for first-line treatment of advanced gastric cancer (SPIRITS trial), has shown that overall survival was better in patients treated with SP than with S-1 alone. In the present retrospective biomarker study, we aimed to develop a methodology to identify the patients with advanced gastric cancer who would respond better to S-1 alone than SP. We studied 120 patients who received S-1 alone or SP for first-line chemotherapy for advanced gastric cancer, and quantitatively evaluated mRNA levels of thymidylate synthase (TS), thymidine phosphorylase (TP), orotate phosphoribosyltransferase (OPRT), dihydropyrimidine dehydrogenase, vascular endothelial growth factor-A, and epidermal growth factor receptor in paraffin-embedded specimens of primary tumors. Multivariate survival analysis in patients who received S-1 monotherapy (66 patients) demonstrated that low TP expression (hazard ratio: 2.55 (95% CI: 1.33 to 4.89)), low TS (2.71 (1.36 to 5.37)), and high OPRT (0.33 (0.13 to 0.86)) were significant predictors of long overall survival. In patients with lower expression of both TP and TS ($n = 23$) than their cutoff values, the S-1 alone group ($n = 15$) had longer overall survival than the SP group ($n = 8$; median overall survival, 18.2 months vs. 9.4 months), whereas the frequency of overall adverse events in the S-1 alone group tended to be lower than that in SP group. Our results suggest that these biomarkers are useful for selection of patients with advanced gastric cancer in whom treatment with S-1 alone will yield survival benefit.

Gastric cancer is more prevalent in East Asia, Eastern Europe and Central and South America than in other areas. Worldwide, gastric cancer ranks second among all causes of death from cancer, with about 700,000 confirmed deaths annu-

Key words: advanced gastric cancer, S-1, cisplatin, predictive marker, fluorouracil-metabolizing enzymes

Abbreviations: SP: S-1 plus cisplatin; TS: thymidylate synthase; TP: thymidine phosphorylase; OPRT: orotate phosphoribosyltransferase; DPD: dihydropyrimidine dehydrogenase; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor; FFPE: formalin-fixed, paraffin embedded; CDHP: 5-chloro-2,4-dihydropyrimidine

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ally.^{1,2} In Japan, this cancer is one of the most frequent causes of death from cancer, despite dramatic advances in diagnosis and treatment.³ Outcomes are extremely poor in patients with unresectable gastric cancer, with the median survival ranging from 3 months to 5 months with best supportive care.⁴⁻⁶

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate at a molar ratio of 1:0.4:1. CDHP reversibly inhibits the activity of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for the degradation of fluorouracil. Therefore, high concentrations of fluorouracil in serum and tumors are maintained for prolonged periods. Potassium oxonate blocks the phosphorylation of fluorouracil in the gastrointestinal tract, decreasing gastrointestinal toxic effects, the largest dose-limiting toxicity of fluorouracil.⁷ Phase II studies of S-1 reported responses of 44-54% in patients with advanced gastric cancer.⁸⁻¹⁰ S-1 is mainly used as first-line treatment for this type of cancer in Japan. Cisplatin is also an important chemotherapeutic drug in the treatment of advanced gastric cancer.

In our previous phase III study on S-1 plus cisplatin (SP) versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial), median overall survival was significantly longer in patients assigned to the SP group (13.0