IMPACT OF THE EXPRESSION LEVELS OF FLUOROPYRIMIDINE PATHWAY GENES ON TREATMENT OUTCOMES FROM ADJUVANT S-1 THERAPY IN GASTRIC CANCER

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Aim: Adjuvant S-1 therapy improves survival in patients with curatively resected gastric cancer (GC). However, little is known about the predictive or prognostic markers related to treatment outcomes from adjuvant S-1. Accordingly, we analyzed the protein and mRNA expression profiles of fluoropyrimidine pathway genes [thymidylate synthase, dehydropyrimidine dehydrogenase (DPD), thymidine phosphorylase and orotate phosphoribosyltransferase] to find markers related to treatment outcomes of adjuvant S-1.

Methods: One hundred eight-four patients who had received curative gastrectomy and adjuvant S-1 were included. Immunohistochemistry (IHC) and real-time polymerase chain reaction (RT-PCR) were performed to measure the protein and mRNA levels of 4 genes from the formalin-fixed paraffin-embedded specimens.

Results: In univariate analysis, low DPD protein expression in tumor (DPD IHC score < 10) had a trend to be related to worse 5-year disease-free survival DFS (77.6% vs. 88.0%; P = 0.068). The measurement of mRNA levels also showed that low DPD gene expression [1st (lowest) quartile] in tumor is related to poor DFS (68.9% vs. 89.6%; P < 0.001), compared with 2nd-4th quartiles harboring higher DPD expression. In multivariate analyses, low DPD protein expression [hazard ratio (HR) 2.32; P = 0.030] or low DPD gene expression (HR 3.67; P = 0.001) was related to worse DFS, irrespectively of other clinical variables. Protein or mRNA levels of other genes were not related to S-1 treatment outcomes. Although statistically insignificant, it seemed like relative dose intensity (RDI) or toxicities were related to DPD mRNA expression [1st quartile vs. 2nd-4th quartiles: RDI, 83.9% vs. 89.4% (P = 0.157); non-hematologic toxicities (grade ≥ 3), 28.9% vs. 16.4% (P = 0.068)].

Conclusions: When receiving adjuvant S-1 therapy, GC patients with high DPD expression in tumor did not have inferior outcome to those with low DPD expression. Instead, low mRNA or protein expression of DPD was related to poor DFS. Less administration of S-1 due to toxicities may have lead to this unexpected inferior treatment outcome in patients with low DPD levels.

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