LOW LEVEL OF THYMIDYLATE SYNTHASE GENE EXPRESSION IN TUMOR TISSUES IS ASSOCIATED WITH RESPONSE TO PREOPERATIVE CHEMORADIOThERAPY INCLUDING S-1 OR UFT IN PATIENTS WITH RECTAL CANCER

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Aim: Preoperative chemoradiotherapy (CRT) including 5-fluorouracil-based oral drug, S-1 or uracil/tegafur (UFT), significantly decreases local recurrence in locally advanced rectal cancer. However, reliable biomarkers to predict the response remain to be established. In the present study, we examined the association of the response to CRT with the expression levels of 18 drug-related genes in tumor tissues.

Methods: Eighty two patients with locally advanced rectal cancer who received preoperative CRT with UFT or S-1 (+ bevacizumab) for 5 weeks were analyzed. We assessed pathological tumor response according to the Japanese classification of colorectal carcinoma criteria. A patient with Grade 2 or 3 was defined as a responder. The mRNA expressions of pyrimidine-related enzymes, reduced folate-related enzymes and radiation-related enzymes (18 genes) in tumor biopsy specimens before CRT were quantitatively evaluated using a RT-PCR assay. The relationships between tumor response and gene expression levels were analyzed. The patients were divided into low and high TYMS groups using the cut-off value determined by the receiver operating characteristic curve.

Results: Pathological response was observed in 72% (59/82) of the patients. There was no significant difference in response rates among clinical parameters. The gene expression level of thymidylate synthase (TYMS) was significantly higher in nonresponders than in responders (p = 0.028). There were no significant associations of tumor response with the expressions of other genes such as folylpolyglutamate synthase (FPGS) and hypoxia inducible factor 1 alpha subunit (HIF1A). In high TYMS group (response rate: 48% (10/21)), the gene expression level of FPGS and HIF1A were higher in nonresponders than in responders (p = 0.035 and p = 0.036, respectively).

Conclusions: The TYMS gene expression levels in tumor tissues may be useful for predicting the efficacy of preoperative CRT including S-1 or UFT in patients with rectal cancer. In the patients with rectal cancer having high expression of TYMS, combination chemotherapy with leucovorin may be required in order to potentiate TYMS inhibition of 5-FU-based drug.

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