P2-086 BSTB: Prognostic Factors Posters, Tue, Sept 4

Predictive value of thymidylate synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase and orotate phosphoribosyl transferase expression in tumor tissue, regarding the efficacy of postoperatively administered UFT (Tegafur + Uracil) in patients with non-small cell lung cancer

Miyoshi, Takanori[1] Kondo, Kazuya[1] Toba, Hiroaki[1] Nagao, Taeko[1] Yoshida, Mitsuteru[1] Hirose, Yukiko[1] Kenzaki, Koichiro[1] Sakiyama, Shoji[1] Takehisa, Masatsugu[2] Tangoku, Akira[1]

[1] Department of Oncological and Regenerative Surgery, Institute of Health Bioscience, University of Tokushima Graduate School, Tokushima, Japan [2] Department of Surgery, Tokushima Hospital, Tokushima, Japan

Introduction: UFT (Tegafur + Uracil) has been reported to be effective for postoperative adjuvant chemotherapy of non-small cell lung cancer (NSCLC) in randomized prospective study. Recently, many clinical studies have revealed that the effect of UFT was effective for cancer with a low activity of Thymidylate Synthase (TS) and Dihydropyrimidine Dehydrogenase (DPD). Firstly, we studied the correlation between the activity and the mRNA expression of TS and DPD in NSCLC. Secondly, we also examined the relationship between TS and DPD protein expression and several data including prognosis in NSCLC patients. In this study, we examined the mRNA expression of TS, DPD, thymidine phosphorylase (TP) and orotate phosphoribosyl transferase (OPRT) from the paraffin-embedded tissue samples.[Patient] Eighty patients underwent complete surgical resection and administered UFT after operation in NSCLC from 1993 to 2001 at the University of Tokushima-affiliated hospital for the first and second studies. Sixty-five patients underwent same as above in NSCLC from 1988 to 2004 for this third study.

Method: Firstly, the activity of TS was determined by the FdUMP binding assay combined with gel filtration. The activity of DPD was determined by the radio-enzymatic assay. And the mRNA expression of TS and DPD was examined by real time RT-PCR method. Secondly, TS and DPD protein expression in tumor tissues was evaluated by immunohistochemical staining (IHC) by LSAB method. For this study, mRNA was isolated from paraffin-embedded specimens. A quantitative real-time reverse transcription-PCR method (TaqMan) was used to measure the expression of TS, DPD, TP and OPRT genes (DTP method). We analyzed whether there was a relationship between these genes expression and post-operative survival in NSCLC.

Result: There was not the relationship between the quantity of each gene expression and stages. The mRNA expression of DPD and TS was correlated to the activity of DPD and TS (r=0.846, 0.757). TS negative expression group had a significantly better prognosis than TS positive expression group (p<0.001) by IHC. Especially the tendency was remarkable in pStage I (10-year survival rate: 95.5% vs22.7 %). There was not a relationship between DPD expression and post-operative survival in NSCLC. TP low expression group (<5.5) had a significantly better prognosis than TP high expression group (>5.5) (p=0.03) by DTP method. There was not a relationship between TS, DPD and OPRT expression and post-operative survival in NSCLC. Though it was not significant p value, TS low expression group (<1.0) had a better prognosis than TS high expression group (>1.0) by DTP method. This result by DTP method was similar to the result by IHC.

Conclusions: Oral administration of UFT in a postoperative adjuvant setting yields a significant improvement in survival in patients with TS negative expression by IHC or TS low expression group by DTP method, especially in pathological stage I NSCLC. TP low expression group had a significantly better prognosis. The high or low expression of DPD and OPRT did not let influence extend to prognosis in NSCLC. Therefore, the uracil of UFT may be able to inhibit DPD activity, and there is a possibility that it can promote an effect of 5-FU.

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Elevated levels of thioredoxin (Trx) in serum correlate with poor outcome in docetaxel (doc)/cisplatin (cis)-treated stage IV non-small-cell lung cancer (NSCLC) patients (p)

Molina, Miguel A.[1] de las Peñas, Ramon[2] Alberola, Vicente[3] Blasco, Ana[4] López-Vivanco, Guillermo[5] Brea, Marta L.[6] González-Larriba, José-Luis[7] Salazar, Fernanda[1] Ramírez, José L.[1] Rosell, Rafael[1]

[1] Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain [2] Hospital Provincial de Castellón, Castellón, Spain [3] Hospital Arnau de Vilanova, Valencia, Spain [4] Hospital General Universitario de Valencia, Valencia, Spain [5] Hospital de Cruces, Baracaldo, Spain [6] Hospital Marqués de Valdecilla, Santander, Spain [7] Hospital Clínico San Carlos, Madrid, Spain

Background: Chemotherapy causes the production of reactive oxygen species (ROS), which facilitates cancer cell death. Trx protein functions as a ROS scavenger and a negative regulator of apoptosis signal regulating kinase-1 (ASK-1). High levels of Trx are associated with chemoresistance. 14-3-3σ proteins are involved in cell cycle control and protein trafficking.

Methods: Trx ELISA and 14-3-3σ methylation-specific PCR were performed in baseline serum from 107 stage IV NSCLC p treated with doc/cis.

Results: Median age, 60 (range, 32-79); male, 87 (81.3%). PS: 0, 27 (25.2%); 1, 80 (74.8%). Adenocarcinoma, 46 (43.8%); squamous cell carcinoma, 40 (38.1%); 21 p had large cell or unspecified histology. Complete response, 1 p; partial response, 20 p; overall response rate, 20%. Median Trx level, 97.4 (range, 18.8-763.1). Serum was available for 14-3-3σ methylation analysis in only 88 p. 14-3-3σ was methylated in 43 p (48.9%). A significant correlation was observed between 14-3-3σ methylation status and Trx levels (Table). 4 p with methylated and 17 with unmethylated 14-3-3σ had Trx levels >182.8 (P=0.003). Median Trx levels were 103.5 in responders and 94.3 in non-responders (P=0.96). Time to progression (TTP) was 5.6 months (m) for 27 p with Trx <49.6, 4.4 m for 53 p with Trx 49.6-182.8, and 3.8 m for 27 p with Trx >182.8 (P=0.02). In a Cox multivariate analysis, Trx levels emerged as an independent variable for TTP when 14-3-3σ was included in the model. Hazard ratios: 1.3 for PS1 (P=0.84); 1.05 for 14-3-3σ unmethylated (P=0.22); 1.4 for Trx 49.6-182.8 and 1.95 for Trx >182.8 (P=0.04).

	TRX Levels	Trx Levels	Trx Levels
14-3-.3 sigma	< 49.7	49.7-182.8	>182.8
methylated	11 (25.6%)	28 (65.1%)	4(9.3%)
	(47.8%)	(63.6%)	(19%)
unmethylated	12 (26.7%)	16 (35.6%)	17 (37.8%)
	(52.2%)	(36.4%)	(81%)

Conclusions: Serum Trx levels can predict TTP in doc/cis-treated p. The additional role of 14-3-3σ methylation may be more clearly demonstrated in cis/gemcitabine regimens.