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REVIEW ARTICLE

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Challenges in predicting the clinical outcome in S-1-based chemotherapy for gastric cancer patients

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Abstract S-1 has been considered to be a key drug in the treatment of advanced gastric cancer in Japan as a standard option of chemotherapy. Interindividual variation in the enzymes of the S-1 metabolic pathway can affect the extent of S-1 metabolism and impact the efficacy of S-1-based chemotherapy. In this review, the role of the "candidate" genetic factors affecting the therapeutic efficacy of S-1 is discussed with a special emphasis on polymorphism and gene expressions involved in the S-1 metabolic pathway, including CYP2A6, thymidylate synthase, thymidine phosphorylase, and orotate phosphoribosyltransferase. The predictive values of these candidates might be overcome with drugs combined with S-1. Pharmacogenetic studies based on a "global" approach by DNA microarray are promising to identify gastric cancer patients with both survival benefit and clinical benefit more accurately than those based on the "candidate" approach, especially for S-1 combination therapy. Large and controlled studies are needed to justify changes in the chemotherapeutic strategies, from "one-size fits all" to "tailor-made."

Key words CYP2A6 · Thymidylate synthase · Dihydropyrimidine dehydrogenase · Thymidine phosphorylase · Orotate phosphoribosyltransferase · Pharmacogenetics

Introduction

A growing body of evidence suggests that interindividual variation in drug-metabolizing enzymes, DNA repair enzymes, or angiogenic enzymes may affect anticancer drug efficacy.[1,2] However, whether the pharmacogenetic variations are useful in predicting drug response and survival to specific chemotherapy regimens remains unknown. Determination of significant associations between gene expressions and defined clinical endpoint (e.g., survival and response) may improve the prediction of treatment success and thereby the tailoring of chemotherapy.

S-1 (Taiho Pharmaceutical, Tokyo Japan) is an oral anticancer agent combined with tegafur (FT), 5-chloro-2,4-dihydroxipyridine (CDHP), and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.[3] A randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin versus S-1 alone in advanced gastric cancer showed significant noninferiority of S-1 to 5-FU-alone regimen (JCOG9912).[4] Another randomized phase III study of S-1 alone versus S-1 plus cisplatin in the treatment for advanced gastric cancer demonstrated significant survival benefit in patients treated with S-1 plus cisplatin.[5] Based on the results obtained from these randomized phase III trials, S-1 has been considered to be a key drug in the treatment of advanced gastric cancer in Japan as a standard option of chemotherapy. Unfortunately, S-1 combination chemotherapies are often toxic or debilitating, and therapeutic responses can vary. Accurate prediction of response to chemotherapy would allow a tailored regimen that maximizes clinical response while limiting the adverse effects of chemotherapy.

In this article, we provide an update on pharmacogenetics as applied to the S-1-based chemotherapy for patients with gastric cancer. We focused on the "candidate" factors that affect the therapeutic efficacy of S-1-based chemotherapy with a special emphasis on gene expression involved in the S-1 metabolic pathway.

Metabolic pathway of S-1

Tegafur (FT) is converted into 5-FU mainly by cytochrome P450 (CYP450) enzymes in the liver. CYP2A6 is the main CYP450 enzyme involved in tegafur activation, but CYP1A2 and CYP2C8 also play a significant role[6] (Fig. 1).

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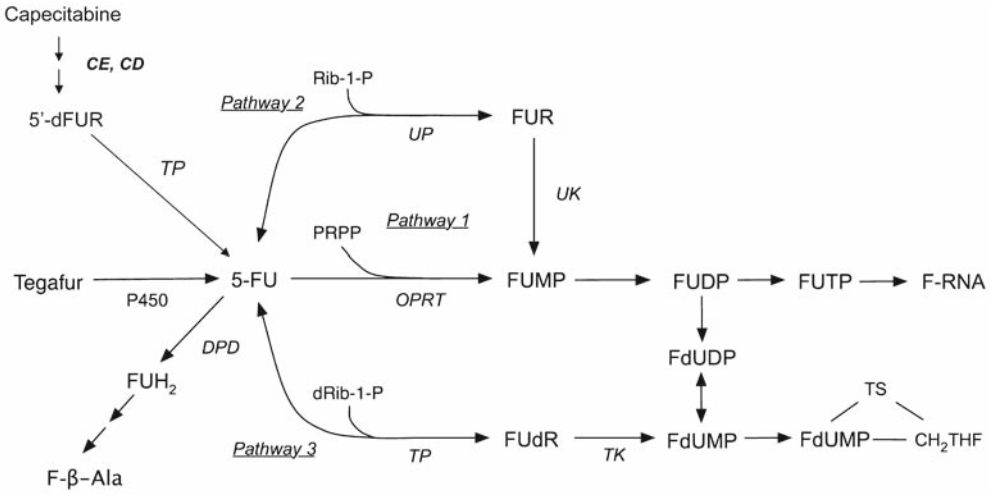

Fig. 1. Metabolic pathway of fluorouracil (5-FU) and 5-FU analogues including tegafur. For explanation of symbols and metabolic pathways, see text. (From Ichikawa[1])

In humans, 80%–90% of the administrated 5-FU is catabolized rapidly to the inactive metabolite α-fluoro-β-alamine via dihydrofluorouracil (FUH_2) by the first and rate-limiting enzyme, dihydropyrimidine dehydrogenase (DPD)[7] (see Fig. 1). 5-FU degradation occurs in all tissues, including tumor tissues, but is greatest in the liver.[8] The main mode of action of 5-FU is considered to be through its active metabolite, 5-fluoro-uridine-5′-triphosphate (FUTP) or 5-fluoro-2′deoxyuridine-5′-monophosphate (FdUMP). FUTP can be incorporated into RNA, whereas FdUMP suppresses thymidylate synthase (TS), an essential DNA de novo synthetic enzyme that catalyzes the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP).[9,10] FdUMP and TS form covalent ternary complexes with 5,10-methylenetetrahydrofolate (5,10-CH_2-FH_4) that subsequently inhibit DNA synthesis (see Fig. 1).

The anabolic conversion of 5-FU into nucleotides such as FUTP or FdUMP is essential for its action, as illustrated in Fig. 1: (1) Pathway 1: directly to FUMP by orotate phosphoribosyltransferase (OPRT) in the presence of 5-phophoribosyl-1-pyrophosphate (PRPP); (2) Pathway 2: indirectly to FUMP in a sequence of reactions with conversion of 5-FU to 5-fluorouridine (FUR), catalyzed by uridine phosphorylase (UP) in the presence of ribose-1-phosphate (Rib-1-P); and (3) Pathway 3: indirectly to FdUMP by 2′-deoxy-5-fluorouridine (FUdR), catalyzed by thymidine phosphorylase (TP) in the presence of deoxyribose-1-phosphate (dRib-1-P).[11] In humans, the preferential use of the OPRT pathway (Pathway 1) was revealed to correlate with a higher sensitivity to 5-FU.[11]

The relative expression of these enzymes participating in the 5-FU metabolic pathway may be related to treatment efficacy and toxicity. In general, expression of high DPD, high TS, or low OPRT in gastrointestinal cancers would be expected to predict a poor response to 5-FU based chemotherapy and to uracil/tegafur (UFT) in advanced colorectal cancer patients.[11,12]

Prediction of clinical outcome in S-1 monotherapy

CYP2A6

CYP2A6 is a polymorphic enzyme that shows considerable interindividual variability in activity for the representative substrate nicotine.[6] The CYP2A6*4 is known to cause a lack of enzymatic activity.[13] The CYP2A6*7 and CYP2A6*9 alleles decrease enzymatic activity by altering catalytic function and protein expression, respectively.[13] The distribution of these polymorphisms shows large interethnic differences, and the frequencies of these mutant alleles are higher in Japanese than in whites.[13] Therefore, it is postulated that the efficacy of CYP2A6 to metabolize FT is higher in whites than in Japanese.

We examined the contributions of CYP2A6 genotype (CYP2A6*4, *7, and *9), plasma CDHP levels, and patient characteristics to the pharmacokinetics (PK) of FT and 5-FU in 40 Japanese cancer patients.[14] The oral clearance (CL/F) of FT was associated only with the CYP2A6 genotype (analysis of variance, $P = 0.000891$, $R^2 = 0.51$). The CL/F of FT seen in patients with one-variant allele (*1/any) and two-variant alleles (*4/*4, *4/*7, *4/*9, *7/*7, *7/*9, and *9/*9) was significantly lower than that seen in the wild type (*1/*1), respectively. The AUC_{0-8} for 5-FU correlated with only the $AUC_{0-\infty}$ for CDHP ($P = 0.00579$, $R^2 = 0.44$). The AUCs for 5-FU and CDHP correlated with creatinine clearance ($P = 0.0160$, $R^2 = 0.14$ and $P = 0.000560$, $R^2 = 0.27$, respectively).

These results indicated that the CYP2A6 genotype statistically correlated with tegafur pharmacokinetics, and not with 5-FU pharmacokinetics. Thus, renal function might directly affect CDHP pharmacokinetics, resulting in the increase of plasma 5-FU after administration of S-1, given that more than 50% of CDHP is eliminated in the urine.[15] To our best knowledge, there is little information about the association between CYP2A6 genotype and clinical outcome in patients treated with S-1-based chemotherapy.

Thymidylate synthase

We previously demonstrated that the median value of TS gene expression in responding tumors was statistically lower than that in nonresponding cases in 27 metastatic gastric patients treated by S-1 monotherapy.[16] Another study including 59 patients confirmed the predictive values for response and survival of TS gene expression in S-1 treatment for metastatic gastric cancer.[17] Patients with tumors with low TS gene expression survived longer than those with tumors with high TS gene expression, with statistical significance. Miyamoto et al. reported that S-1 showed antitumor effects in terms of tumor shrinkage and survival, regardless of the expression status of TS, when TS expression was evaluated by immunohistochemical methods using antirecombinant human TS polyclonal antibody.[18] This finding did not agree with our results. A possible explanation might be the difference in methodology for measuring TS expression, because the detection method in gene expression is a more quantitative and sensitive evaluation method than the immunohistochemical method.[1]

Dihydropyrimidine dehydrogenase

CDHP contained in S-1 reversibly inhibits the activity of DPD in the liver, producing a higher plasma 5-FU concentration, followed by the increment of antitumor effect.[3,12] Takechi et al. demonstrated that CDHP inhibits 5-FU degradation through the inhibition of intratumoral DPD activity and enhances 5-FU cytotoxicity in human cancer cells both in vitro and in vivo.[19] Actually, the antitumor effect of S-1 for gastric cancer was not influenced by intratumoral DPD gene expression, as indicated in three independent studies.[17,20,21] Miyamoto et al. also reported that patients with positive DPD showed a slightly higher response rate and longer survival than those with negative DPD, but without statistical significance, when DPD expression was evaluated by the immunohistochemical method.[18] In 61 patients with gastric scirrhous carcinoma, the response rate was significantly higher in patients with DPD-positive tumors than in those with DPD-negative ones in the S-1 group, as compared with the 5-FU group.[22] Together with these results, S-1 is thought to have antitumor activity even in highly DPD expressed tumor, which is essentially resistant to fluoropyrimidine without the DPD inhibitor.

Orotate phosphoribosyltransferase

S-1 contains Oxo, which decreases the levels of FUMP and 5-FU incorporated into RNA (F-RNA) by about 70% in the small intestine through the inhibition of OPRT activity.[23] Oxo is distributed at high levels in the digestive tract after oral administration and thus reduces 5-FU-induced gastrointestinal toxicity such as diarrhea.[24] If Oxo in plasma inhibits the intratumoral OPRT, the antitumor effect of S-1 might be diminished and the predictive value of OPRT expression might be overcome. We indicated that OPRT gene expression in the gastric tumor is related to higher response rate and longer survival in 59 gastric cancer patients treated with S-1,[1] as well as in colorectal cancer patients treated with UFT, which does not include Oxo.[11] These data were concordant with the in vivo study to demonstrate that the decrease in the levels of FUMP and F-RNA is limited to 0%–20% in tumor regions, without affecting the antitumor effect of 5-FU.[23]

"Polygenic" approach

Each gene expression, such as TS and OPRT, involving the 5-FU metabolic pathway just discussed might be useful for predicting the clinical outcome in S-1 monotherapy. However, these genes involving the 5-FU pathway do not act in isolation, even though genes do not actually work in the 5-FU metabolic pathway. The use of more than single gene expression, such as the combination of TS, DPD, and TP, or DPD and OPRT, has been reported to permit the identification of a high percentage of responding patients in colorectal cancer.[11,12,25]

We evaluated whether the response to S-1 treatment could be predicted in terms of gene expression of five genes involved in the 5-FU pathway (TS, DPD, OPRT, TP, and UP).[17] In univariate analyses, low TS, high OPRT, and low TP were significantly associated with tumor shrinkage and long survival, whereas DPD and UP gene expression did not correlate with response and survival (Tables 1, 2). Multivariate analyses including five gene expressions revealed

Table 1. Logistic regression analysis for response

Variable	Univariate			Multivariate*		
	OR	95% CI	*P*	OR	95% CI	*P*
DPD	1.20	0.96–1.52	0.122	–	–	
TS	0.005	0.00–0.08	0.002	0.003	0.00–0.25	0.0433
OPRT	63.5	9.64–1137.7	0.0005	46.3	6.51–1316.3	0.0036
TP	0.98	0.96–0.99	0.022	–	–	
UP	1.16	0.98–1.39	0.086	–	–	

Note: in the multivariate analysis, stepwise regression was used to select variables
OR, odds ratio; CI, confidence interval; DPD, dihydropyrimidine dehydrogenase; TS, thymidylate synthase; OPRT, orotate phosphoribosyltransferase; TP, thymidine phosphorylase; UP, uridine phosphorylase
*Probabilities to enter and remove variables were set at less than 0.05 and greater than 0.1, respectively
Source: Ichikawa et al.[17]

Table 2. Cox proportional hazard analysis for survival

Variable	Univariate			Multivariate*		
	HR	95% CI	*P*	HR	95% CI	*P*
DPD	1.08	0.97–1.21	0.1811	–	–	
TS	5.96	2.74–12.93	<0.0001	4.75	2.17–10.34	<0.0001
OPRT	0.58	0.39–0.85	0.0056	–	–	
TP	1.009	1.005–1.013	<0.0001	1.008	1.004–1.012	0.0002
UP	0.94	0.87–1.02	0.1461	–	–	

Note: in the multivariate analysis, stepwise regression was used to select variables
HR, hazard ratio; CI, confidence interval
*Probabilities to enter and remove variables were set at less than 0.05 and greater than 0.1, respectively
Source: Ichikawa et al.[17]

that independent variables were OPRT and TS for response and TS and TP for survival (Tables 1, 2). When OPRT and TS were combined, a significantly increased accuracy rate of 91.5% was seen for response, as compared with 71.5% obtained from the information of TS gene expression. Similarly, an increased hazard ratio of 10.29 was observed for survival in patients possessing low TS and low TP, compared with those with high TS and/or high TP. Thus, the simple combinations of two genes, OPRT and TS for response and TS and TP for survival, may allow identification of gastric cancer patients who will benefit from S-1 chemotherapy.

These results might indicate that antitumor activity, even in S-1 monotherapy, is a polyfactorial event as a result of the combined effect of more than one gene.

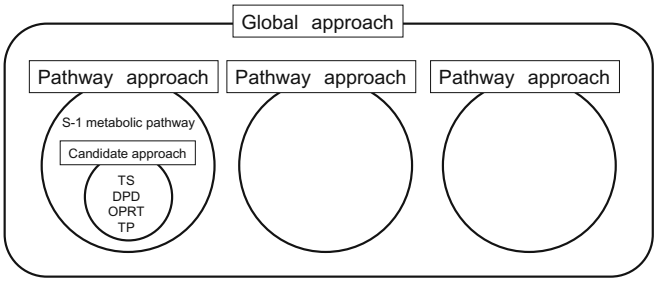

Fig. 2. Pharmacogenetic study is categorized into three approaches including candidate approach, pathway approach, and global approach, in terms of the numbers of evaluated genes and the applied methods

Prediction of clinical outcome in S-1 combination chemotherapy

When S-1 is combined with irinotecan, the predictive value of TS gene expression for clinical outcome is overcome.[16] There was no statistically significant difference in response rate and survival between patients with low TS tumors and those with high TS tumors in 26 patients treated with S-1 combined with irinotecan. Our results were confirmed by Takiuchi et al.[21] There was no relationship between TS gene expression and tumor response in the S-1 and irinotecan treatment group ($n = 11$), with responses being observed in some patients having tumors with high TS gene expression. In vivo studies indicated that TS activity is downregulated by irinotecan in a dose-dependent manner in xenografts with high levels of TS expression, suggesting that irinotecan results in an environment in which S-1 is more likely to exert its antitumor effect.[21]

The combination of S-1 and docetaxel exhibited greater growth-inhibitory effects in human tumor xenograft models than the treatment of S-1 alone or docetaxel alone.[26] This synergistic antitumor effect was greater in the combination of S-1 and docetaxel than that of 5-FU and docetaxel. The expressions of TS and DPD were decreased 50% and 73% of control levels, respectively, and that of OPRT was increased by 3.9 fold at the protein level, by the treatment of docetaxel in combination with 5-FU.[26] These findings suggested that biochemical modulation of the two drugs had occurred. That is, predictive values of "candidate" gene expressions, which are selected in S-1 monotherapy, for clinical outcome might be overcome when S-1 is combined with other anticancer agents such as irinotecan or docetaxel.

Future perspective

Pharmacogenetic study to predict clinical outcome is categorized into the following three approaches: (1) the candidate approach, evaluating several genes to be narrowed down from the information previously reported in vivo and in vitro studies, by reverse-transcriptase polymerase chain-reaction (RT-PCR) or real-time RT-PCR; (2) the pathway approach, evaluating a few dozen genes to be involved in the pathway, such as S-1 metabolic pathway, apoptosis pathway, or cell-cycle pathway, by low-density array[27]; and (3) the global approach, identifying potential chemoresistance-related genes within a panel of hundreds to thousands of genes by DNA microarray.[2] Potential candidates such as TS, OPRT, and TP have been identified by the candidate approach (Fig. 2).

Most enzymes function in complex networks with several regulatory mechanisms. It is unlikely that any one candidate with modest effects on enzyme function will affect treatment outcome, whereas the combination of several candi-

dates within the same pathway might result in significant disturbance. A "polygenetic approach" by two genes in combination in the S-1 metabolic pathway is a good example for the pathway approach.

In addition, currently S-1 monotherapy is not recommended for the control arm in randomized clinical trials in patients with advanced gastric cancer. The use of multidrug combinations of S-1 with other drugs has become more standard. Thus, cisplatin has been administered in combination with S-1, resulting in significantly prolonged overall survival over 12 months.[5] New agents, such as the monoclonal antibodies herceptin (an epidermal growth factor receptor inhibitor) and bevacizumab (a vascular endothelial growth factor inhibitor) have shown promising clinical benefit for patients with advanced gastric cancer.

DNA microanalysis can be used to identify gene expression within a panel of hundreds to thousands of genes. In initial studies, microarray analysis has identified candidate genes for further investigation that are differently expressed between normal gastric mucosa and gastric cancer.[28] Microarray assays have also identified potential prognostic or predictive biomarkers even in combination chemotherapy; however, many more have yet to be evaluated.[29,30] With the growing number of treatment options and varying treatment response, a multigene assay could be developed and would potentially have tremendous clinical utility and benefit in patients with advanced gastric cancer.

The final goal of the individualization is to select the right patient and the right drug and to determine the right dose of drug. Studies examining the gene expression involved in the metabolism of S-1 in tumor tissues can serve as surrogate markers predictive of tumor shrinkage and survival. Studies on prediction of adverse events and determination of optimal dosing of S-1 by genotyping have also been under way.[14,31] Integration of these studies is anticipated to realize the individualization of S-1-based chemotherapy.

Conclusions

To date, relatively small retrospective studies have identified TS, OPRT, and TP as potential candidates to predict the clinical outcome in S-1 monotherapy. The complex nature of cytotoxic metabolism, which often involves multiple players, and the relative small number of patients in the published studies pose significant limitations in our current knowledge of gastric cancer pharmacogenetics. Larger well-designed studies are needed to confirm the foregoing findings, as well as the investigation of other potential candidates that might not have shown significant associations with clinical outcome in the aforementioned early studies. We expected further research to yield important clues that might help guide a clinician make real-time decisions to treat a patient with a particular regimen – an S-1 based regimen or non-S-1 regimen, S-1 monotherapy or S-1-based combination therapy, or the best drug to combine with S-1.

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