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Review

Current Status of Therapeutic Drug Monitoring of 5-Fluorouracil Prodrugs

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Abstract. *In recent years, therapeutic drug monitoring (TDM) of intravenous administration of 5-fluorouracil (5-FU) has resulted in reduced toxicity and improved efficacy. Prodrugs of 5-FU were developed to reduce toxicity, extend the duration of action, and increase tumour selectivity of 5-FU. These drugs are important in daily practice because of their ease of administration. Dose adjustment of 5-FU prodrugs by TDM is expected to reduce its toxicity and improve its efficacy. This review focuses on data from a recent study of personalized treatment using TDM of 5-FU and its prodrugs.*

Therapeutic drug monitoring (TDM) refers to measuring the concentration of a drug in a biological sample to individualize the drug dose, in order to improve drug efficacy and reduce toxicity (1). This method has been mainly developed and put into practical use for antibacterial drugs and antiepileptic drugs and has shown beneficial results. In recent years, TDM has been considered an important strategy to optimize the therapeutic effects of anticancer drugs with a very narrow therapeutic index and high cytotoxicity (2).

In current gastrointestinal cancer care, 5-fluorouracil (5-FU) is a key drug in cancer treatment, and is the backbone of chemotherapy, especially for colorectal cancer treatment. The dosing schedule originally involved administering a bolus and evolved into a continuous intravenous schedule, followed by an intermittent intravenous schedule, and then a bolus and intermittent intravenous hybrid schedule. In addition, treatment results were dramatically improved using a combination regimen with oxaliplatin or irinotecan or a combination including molecular-targeted drugs such as bevacizumab, cetuximab, and panitumumab. In a recent report, 5-FU was also used for neoadjuvant and adjuvant chemotherapy and showed good therapeutic results (3, 4).

In daily practice, the dosage of 5-FU is generally calculated based on the patient's body surface area (BSA). However, BSA has been shown to be an insufficient predictor of systemic drug exposure (5-7). In addition, recent studies have reported a relationship between drug exposure, toxicity and efficacy (8). In previous reports, the response rate was significantly improved and adverse events were reduced for patients who underwent TDM-based 5-FU dose adjustment compared with patients treated with conventional 5-FU administration (9-12). Appropriate adjustment of the 5-FU blood concentration can improve both the safety and efficacy of treatment. This review focuses on recent studies of personalized treatment using TDM of 5-FU and its prodrug.

5-FU Prodrugs

A prodrug is defined as a compound that undergoes biotransformation before exhibiting its therapeutic effect (13). By converting a drug into a prodrug, the chemical stability, solubility, oral bioavailability, blood-brain barrier permeability, tissue-selective activation, toxicity reduction, optimization of action speed or duration, and acceptability can be improved (14, 15). Prodrugs of 5-FU were developed to reduce toxicity, extend the duration of action, and increase tumour selectivity.

Tegafur. Tegafur was developed by Hiller *et al.* (16). It is rapidly absorbed from the gastrointestinal tract by oral administration. The absorbed tegafur is metabolized by cytochrome P450, mainly in the liver. Therefore, it is

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gradually converted into 5-FU, and a high concentration of 5-FU persists in the blood and tissue for a long time. Tegafur is also converted to 5-FU by pyrimidine-nucleoside-phosphorylase, which is present in the liver, small intestine, and tumour tissues.

UFT. Tegafur is gradually converted to 5-FU after oral administration but is simultaneously catabolized and degraded by dihydropyrimidine dehydrogenase (DPD). To exert a substantial anti-tumour effect, it is necessary to maintain high levels of 5-FU in the blood and tissues. UFT is a drug that contains uracil, which inhibits the degradation of 5-FU by DPD. It is the first anticancer drug formulated by biochemical modulation (17). The uracil (molar ratio of tegafur: uracil=1:4) contained in UFT competitively inhibits the degradation of 5-FU by DPD but does not inhibit phosphorylation; therefore, the antitumour effect is enhanced. Furthermore, 5-FU and its phosphorylated metabolite are maintained at high concentrations in tumours (18, 19).

S-1. S-1 was developed to enhance the effect of UFT and reduce side effects. It is composed of tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1. Gimeracil inhibits the DPD enzyme more potently (200-fold) than uracil (20). Oteracil is distributed at a high concentration in the gastrointestinal tract and inhibits the phosphorylation of 5-FU, thereby enhancing the antitumour effect and reducing gastrointestinal toxicity (21).

Carmofur. Carmofur was synthesized and developed by Hoshi *et al.* in Japan in 1975 (22). Carmofur releases 5-FU without the intervention of drug metabolizing enzymes such as DPD by attaching a hexyl group to the carbamoyl bond of 5-FU. It is rapidly absorbed from the gastrointestinal tract and gradually releases 5-FU into the blood, lymph, ascites, and tissues. Carmofur is also a very powerful acid ceramidase inhibitor. Ceramide affects the survival, growth, and death of cancer cells (23).

Doxifluridine. Doxifluridine (5'-DFUR) was synthesized by Cook *et al.* in 1976. 5'-DFUR itself has no cytostatic effect and is converted to 5-FU by thymidine phosphorylase (TP), which is abundant in tumour tissues. In addition, TP activity is considered to be higher in tumour tissues than in surrounding normal tissues, and it is thought that 5-FU is selectively increased in tumour tissues. TP is a unique enzyme and was found to be the same protein as platelet-derived endothelial cell growth factor, which has an angiogenic action (24, 25). Its expression level has been reported to correlate with vessel density and prognosis (26, 27).

Capecitabine. Capecitabine is converted to 5-FU *via* a three-step activation. First, capecitabine is metabolized in the liver by carboxylesterase, which has low activity in the intestinal epithelium. Next, it is sequentially metabolized by cytidine deaminase, which is highly expressed in the liver and tumour tissue. Finally, it is converted to 5-FU by TP, which exhibits high activity in tumour tissue. This multi-step metabolism reduces gastrointestinal and bone marrow toxicity and results in high tumour selectivity (28).

Current Status of TDM Measurement Methods

Various blood concentration measurement methods have been developed for the analysis of 5-FU. One commonly method that has been reported for measurement of the blood concentration after 5-FU administration is liquid chromatography-tandem mass spectrometry (LC-MS). This method can also be used to measure metabolites of capecitabine, which is a prodrug of 5-FU (10-12).

However, LC-MS is currently only available in specialized clinical laboratories, and has poor versatility. Recently, an My5-FU immunoassay was developed to rapidly measure 5-FU levels in human plasma (29). The assay is based on the aggregation of nanoparticles, which is inversely proportional to the amount of 5-FU in the sample. The My5-FU assay showed comparable performance to various analysis methods such as LC-MS and other commonly used clinical analysis methods. The My-5FU assay can measure the blood concentration of 5-FU using a general clinical test instrument (30). As a result, TDM has become easier in daily medical care. However, at present, there are only a few reports describing the measurement of the blood concentration of 5-FU prodrugs using this method. It is also necessary to verify that accurate TDM of 5-FU prodrugs can be achieved.

Individualized Treatment with TDM of 5-FU and 5-FU Prodrugs

TDM of 5-FU allows dose adjustment of 5-FU according to the plasma concentration. Some reports have described the clinical effects of this process such as reduced toxicity and improved efficacy (Table I) (9, 31-41). Two 5-FU dose adjustment algorithms have been mainly used in recent reports. The first target for 5-FU is an area under the curve (AUC) of 20-25 mg · h/l, and the second is an AUC of 20-30 mg · h/l. The former algorithm was reported by Gamelin. This is the only prospective randomized TDM study that has been conducted, and demonstrated reduced toxicity and a trend toward improved survival (10). The latter is the dosing algorithm reported by Kaldate (42). Wilhelm quickly reached the target 5-FU AUC, demonstrating that pharmacokinetic variability could be reduced.

However, various research reports have described the measurement of the blood concentration of 5-FU prodrugs using TDM for the purpose of pharmacokinetic verification.

Table I. *Summary of personalized treatment report with TDM of 5-FU.*

Authors (Ref)	Year	Patients	Cancer	Regimen	First 5-FU dosage	TDM analysis	Sampling time	Sampling day (Day)	Dose adjustment	Effectiveness
Santini (31)	1989	170	Head& Neck	5-FU cisplatin	1,000 mg/m^2	HPCL	8a.m, 5p.m	1,2,3,4,5	5-FU AUC 0-3 days was analyzed in real-time to decide the dose of 5-FU. 5-FU reduction between 30 and 50%.	Reduced toxicity. Improvement in ORR.
Gamelin (32)	1998	152	CRC	5-FU,LV	1,300 mg/m^2	NA	NA	NA	The initial dose of 5-FU was adapted weekly according to 5-FU plasma levels.	Reduced toxicity. Improvement in ORR, OS.
Fety (33)	1998	106	Head& Neck	5-FU cisplatin	1,000 mg/m^2	HPLC	8a.m, 5p.m	1,2,3,4	5-FU dose adjustment according to 5-FU AUC0-48 hours.	Reduced toxicity. Response rates were equivalent.
Ychou (34)	2003	53	Head& Neck	LV5FU2	400 mg/m^2/ day bolus 600 mg/m^2/day	HPLC	0 h, 2 h 20 min, 20 h	1,2	Cycle2 dose adjustment depending on cycle 1 toxicity.	Reduced toxicity. No pharmacokinetic variables were significant for OS.
Gamelin (9)	2008	208	mCRC	5-FU,LV	1,500 mg/m^2	NA	3 h,7 h	1	5-FU AUC 20-25 mg•h/l	Fewer grade 3/4 toxicities. Trend to higher survival rate.
Saam (35)	2011	356	CRC	FOLFOX6 FOLFIRI	NA	Immuno-assay (Ondose®)	2 h, end of infusion	1,2	5-FU AUC 20-24 mg•h/l	NA
Capitain (36)	2012	157	mCRC	FOLFOX6	400 mg/m^2/ day bolus 2500 mg/m^2	NA	NA	NA	5-FU AUC 20-25 mg•h/l	Reduced toxicity. Improvement in ORR, OS, PFS.
Kline (37)	2014	84	mCRC	mFOLFOX6	NA	Immuno-assay (Ondose®)	NA	NA	5-FU AUC 20-24 mg•h/l	Reduced toxicity. Improvement in PFS.
Patel (38)	2014	70	mCRC	mFOLFOX6	400 mg/m^2/ day bolus 2,500 mg/m^2	Immuno-assay	2 h,44 h	1,2	5-FU AUC 20-25 mg•h/l	Reduced toxicities.
Wilhelm (39)	2016	75	mCRC	AIO FOLFOX6 FUFOX	NA	Immuno-assay (My5FU®)	18 h, 4 h before the end of infusion	1,2	5-FU AUC 20-30 mg•h/l	Reduced toxicities.
Denda (40)	2016	48	mCRC	mFOLFOX7	2,400 mg/m^2	Immuno-assay (My5FU®)	18 h,36 h	1,2	5-FU AUC 20-30 mg•h/l	Reduced toxicity. Improvement in ORR, OS, PFS.
Deng (41)	2019	153	mCRC	FOLFOX FOLFIRI	NA	Immuno-assay (My5FU®)	NA	NA	5-FU AUC 20-30 mg•h/l	5-FU dose well without an increased 5-FU toxicity.

mCRC: Metastatic colorectal cancer; LV: leucovorin; HPLC: high performance liquid chromatography; TDM: therapeautic drug monitoring; AUC: area under the curve; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

Kochi *et al*. performed TDM of S-1 before and after gastrectomy and reported that the pharmacokinetics of 5-FU did not change regardless of whether partial or total gastrectomy was performed (43). Lacrimal tract disorders caused by S-1 are well-known adverse events. Yasui measured drug concentrations in the plasma and tears, and demonstrated that 5-FU and gimeracil concentrations exhibit a positive correlation (44). This report is expected to contribute to the establishment of preventive measures for lacrimal disorders.

Among 5-FU prodrugs, various studies have been conducted to elucidate the pharmacokinetics of capecitabine, which is used to treat many types of carcinoma. Gieschke reported that 5-FU, 5'-DFUR, and fluoro-β-alanine (FBAL)

Table II. *Summary of personalized treatment report with TDM of 5-FU prodrugs*

Authors (Ref)	Year	Patients	Cancer	Status	5-FU prodrugs	TDM analysis	Sampling time (hour)	Sampling day (Day)	Dosage adjustment	Cotreatment	OS (Months)
Tominaga (48)	2004	1	GC	HD	TS-1	NA	1stHD:0,2,4,6,8,24 2ndHD:1,2,4,72	1,3	100 mg/Day	–	NA
Yamamoto (49)	2005	1	GC	Impaired renal function	TS-1	NA	0,2,4,6,10,24	1,5	120 mg/Day	–	About 2
Tanaka (50)	2005	1	GC	HD	TS-1	GC-MS	0,3,5,24,43,48	1	80-100 mg/Day	–	7,5
Yoshida (51)	2015	1	CRC	DPD-deficient	Capecitabine	HPLC	0,2	1,2,4,6,8	300-1800 mg/Day	Oxaliplatin Bevacizumab	NA
Li (52)	2019	1	CRC	X-linked agammaglo-bulinemia	Capecitabine	NA	NA	NA	1000 mg/m^2	Oxaliplatin Cetuximab	7,5

GC: Gastric cancer; CRC: colorectal cancer; HD: hemodialysis; DPD: dihydropyrimidine dehydrogenase; TDM: therapeutic drug monitoring; GC-MS: gas chromatography-mass spectrometry; HPLC: high performance liquid chromatography; OS: overall survival.

levels in plasma did not necessarily reflect the levels in healthy tissues and tumours after capecitabine treatment (45). Capecitabine is thought to be selectively converted to 5-FU in tumours *via* a cascade of three enzymes. According to measurements of 5-FU blood levels after capecitabine administration, capecitabine is not considered to be converted to 5-FU in the blood. Therefore, inhibitors of the three enzymes have not been examined, and there have been no reports of attempts to measure the blood concentration of 5-FU in the presence of an enzyme inhibitor after administration of capecitabine. However, Yoshida reported for the first time the 5-FU concentration in the blood after a TP inhibitor (5-nitrouracil) was added to a blood sample. The results showed that the 5-FU plasma concentration differed depending on the time from blood collection to measurement, the temperature at the time of measurement, and the presence or absence of the TP inhibitor 5-nitrouracil (46). In view of Yoshida's report, it is preferable to measure the blood 5-FU concentration immediately after blood collection, but this is not practical in actual clinical settings for various reasons. Esther reported that the optimal sampling times for TDM of capecitabine to maximize the information obtained consisted of blood sampling at 0.5, 1, 1.5, 5, and 8 hours after drug administration (47). A risk of incorrect TDM and incorrect dosage adjustment exists because of differences in time, temperature, and the presence of metabolic enzymes. Therefore, it is very important to accurately measure the blood concentration, but further research on this subject is needed.

At present, TDM is being performed to elucidate the pharmacokinetic properties of drugs. However, there are some case reports of dose adjustment of 5-FU prodrugs by TDM (Table II) (48-52). Tanaka reported that TDM of S-1 was used in patients with recurrent gastric cancer undergoing maintenance dialysis to estimate the appropriate S-1 dose and administer treatment. Fifty percent (50 mg/day) or 40% (40 mg/day) of the reference dose of S-1 was orally administered immediately after dialysis every other day, and TDM was performed for a total of 16 blood collection points using gas chromatography. As a result, the AUC at the time of administration of 40 mg/day was equivalent to that at the time of administration of 100 mg/day, which is a safe dose for patients with normal renal function. Treatment was performed with S-1 for a total of 4 months, and 11 cycles of administration every other day were considered one cycle. The only adverse event was mild stomatitis, and control of ascites was possible (50).

Tominaga performed TDM at 31 blood sampling points in patients with gastric cancer liver metastases undergoing maintenance dialysis. As a result, 50 mg/dose, corresponding to 41.7% of the reference dose of S-1 (128 mg/day), was administered immediately after dialysis three times a week, and a response was obtained without adverse events (48). Yoshida performed TDM of capecitabine in a colon cancer patient with DPD deficiency, and the dose was adjusted while observing side effects (51). Li reported that TDM of capecitabine was performed in immunodeficient X-linked agammaglobulinaemia colorectal cancer patients, and the dose was adjusted while focusing on the appearance of toxicity (52).

TDM of 5-FU has begun to be introduced clinically for personalized therapy, while TDM of 5-FU prodrugs has only been performed to elucidate the pharmacokinetic properties.

There are no reports of prospective clinical studies on dose control. Currently, we are entering an era where cancer gene analysis can be used to select appropriate anticancer drugs. However, it is not possible to determine the amount

of anticancer drug by genetic analysis. If serious side effects occur because of the administration of a selected anticancer drug, the treatment must be discontinued. 5-FU is characterized by a narrow therapeutic window and strong exposure-toxicity relationship, which support the use of approaches to monitor drug administration. Individualized treatment with TDM is expected to optimize therapy and will be indispensable for effective cancer gene analysis and treatment in the future.

Conclusion

At present, personalized treatment with TDM of 5-FU prodrugs has not been applied in daily clinical practice. In the future, it will be necessary to consider individualized treatment with TDM in large-scale prospective studies.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Y.H. and Y.Y. contributed to study concept and design, analysis, and interpretation of data, drafting of the manuscripts. T.Y., N.A., G.Y., and F.Y. contributed to the acquisition of data and research performance. S.H. revised the manuscript. All Authors approved the final version of the manuscript.

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