

Tegafur and 5-fluorouracil levels in tears and changes in tear volume in long-term users of the oral anticancer drug S-1

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ABSTRACT

Eye problems are an adverse reaction sometimes found in chemotherapy. Although not life-threatening, they can reduce patients' quality of life. The highest incidence of eye problems is reported for the combination anticancer drug S-1 (tegafur–gimeracil–oteracil), and methods to prevent or treat the eye problems caused by this drug are presently lacking. To determine early detection methods and treatment for adverse ocular reactions, we measured changes in tear volume and levels of tegafur (FT) and 5-fluorouracil (5-FU), an active metabolite of FT, in the tears of patients with long-term use of S-1. A total of 11 patients receiving S-1 monotherapy as adjuvant chemotherapy after gastric cancer surgery were included. Tear volume and FT and 5-FU levels in tears were measured by liquid chromatography with tandem mass spectrometry during a maximum of 8 treatment cycles (48 weeks). For analysis, patients were divided into two groups: “watering eyes” (n=6, complaints of watering eyes at least once during the treatment period) and “no watering eyes” (n=5, no complaints of watering eyes). Both groups exhibited increased FT and 5-FU levels in tears upon initiation of S-1 treatment, and levels rapidly decreased upon discontinuation. Our findings suggest a relationship between FT level in tears and tear volume in patients with long-term S-1 use. The symptom of watering eyes may thus be linked to FT level in tears.

Keywords: S-1, tegafur, 5-fluorouracil, watering eyes, LC-MS/MS

Abbreviations:

5-FU: 5-fluorouracil

FT: tegafur

LC-MS/MS: liquid chromatography with tandem mass spectrometry

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INTRODUCTION

Recent increases in the number of medical drugs and diversification of drug regimens have caused various types of adverse reactions occur. For anticancer drugs, several characteristic

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adverse reactions—which are not necessarily predictable from drug’s mode of action—have been reported due to their expanded indications and subsequent increase in applicable patient numbers. In contrast to established guidelines for the treatment and prevention of common adverse reactions, such as hematotoxicity and gastrotoxicity,¹⁻³ guidelines for adverse reactions that are not life-threatening yet still reduce patients’ quality of life currently are not available. Such reactions often include eye problems.

The oral anticancer drug S-1 comprises tegafur (FT), gimeracil, and oteracil in a molar ratio of 1:0.4:1. FT is a prodrug; 5-fluorouracil (5-FU), a potent inhibitor of DNA biosynthesis, is produced from FT by P450 (CYP2A6) in the liver. Gimeracil is an inhibitor of dihydropyridine dehydrogenase, a metabolizing enzyme of 5-FU, and maintains 5-FU level in blood. Oteracil inhibits the orotate phosphoribosyl transferase that metabolizes 5-FU into 5-fluoronucleotide, thereby reducing or suppressing its adverse effects in the gastrointestinal tract. Eye problems caused by S-1 administration were first reported in 2005 by Esmaeli et al.⁴ Subsequently, ophthalmologists have reported several similar critical and refractory cases.⁵⁻¹² Watering eyes, the most commonly known eye problem caused by S-1, is due to ocular mucositis (conjunctivitis) or stenosis of the lacrimal canal whereas the underlying mechanism has not been accurately elucidated.

Because eye problems are not life-threatening, many patients are left untreated despite their declined quality of life and the risk of lowered visual acuity under exacerbated conditions. Thus, it is important to diagnose at an early stage and to establish the treatment method of watering eyes due to S-1 administration. To this end, some studies have measured 5-FU levels in the blood or tears of patients taking S-1,¹²⁻¹⁴ or surveyed the incidence of watering eyes and subjective symptoms during the period of S-1 treatment.¹⁴⁻¹⁸ However, the relationship between tear volume and drug concentrations in the tears of patients with long-term S-1 use has not yet been assessed. In the present study, we assessed tear volume and FT and 5-FU levels in the tears of patients administered S-1 over several cycles of the treatment from initiation until termination.

METHODS

1. Patients and S-1 treatment regimen

The study population included 11 patients (6 men, 5 women) who received S-1 monotherapy as adjuvant chemotherapy after gastric cancer surgery at the Aichi Cancer Center Hospital, Japan. One cycle of S-1 monotherapy was defined as the administration of S-1 (40 mg/m²) twice a day for 4 weeks without any other anticancer drug, followed by 2 weeks of washout (drug holiday). The cycle was repeated up to eight times. Four patients underwent an irregular treatment schedule due to their clinical condition (2 weeks of S-1 administration followed by 1 week of washout, repeated twice). In addition, a reduced S-1 dose, prolonged washout period, or changes in regimen were made when patients exhibited abnormal clinical test results and/or severe digestive symptoms. Follow-up was conducted until patients completed eight cycles of S-1 treatment or until administration was inevitably discontinued.

2. Tears sampling schedule

Patients were divided into two groups: a “watering eyes” group (those with complaints of watering eyes as a subjective symptom at least once during the treatment period) and a “no watering eyes” group (those with no complaints of watering eyes). All patients were subjected to tear collection on every consultation day. The day prior to initiating S-1 treatment or the first day after the washout period (1 or 2 weeks) was defined as day 0. Day 14 or day 28 was a day in the cycle after starting or restarting treatment.

3. Schirmer's test

Tear volume (from both eyes) was measured using Schirmer's test. Schirmer's test strips (scaled) were purchased from AYUMI Pharmaceutical Corporation (Tokyo, Japan). The tip of the strip was held in a hook-like conformation on the lower eyelid of outer one-third of the conjunctival sac of each eye. After 5 min, the strip was removed and the length (mm) of the wet portion was measured; 1 mm of wetted strip was considered equivalent to 1 μ L tear volume, as previously described.¹⁹ In cases where the entire strip length (35 mm) was wetted within 5 min, the tear volume was estimated proportionally for 5 min. The strips used to collect tears and measure its volume were stored in sample tubes at -30°C until quantification of FT and 5-FU levels by LC-MS/MS.

4. Quantitation of FT and 5-FU levels in tears

The Schirmer's test strip obtained from the left eye was used for quantification of FT and 5-FU. The amounts of FT and 5-FU absorbed by the Schirmer's test strip were measured using LC-MS/MS according to the method described by Remaud et al²⁰ with slight modifications. A total of 500 μ L water and 5 μ L 5-chlorouracil (5-CU, 100 ng/mL; internal standard) were added to the strip, and it was slowly shaken for 5 min. The water extract was filtered using a CATION-SR filter (3M, MI, USA) and then evaporated until dry using a Savant SPD1010 SpeedVac Concentrator (Thermo Scientific, MA, USA). The residue was dissolved in 50 μ L 50% methanol and centrifuged (15,000 rpm, 5 min). A 5 μ L aliquot of the obtained supernatant was analyzed by LC-MS/MS (Prominence UFLC, Shimadzu Corporation, Kyoto, Japan; API 4000, AB Sciex Pte. Ltd., MA, USA) using a Hypercarb column (150 mm \times 2.1 mm, 5 μ m, Thermo Scientific). Mobile phases A and B were 0.1 mM ammonium bicarbonate aqueous solution (pH 8.0) and acetonitrile, respectively. The flow rate was maintained at 0.2 mL/min. From 0 to 2 min, the mobile phase B was 12%, which increased to 70% over 3 min and then remained constant for 5 min. Thereafter, it returned to 12% over 5 min. For mass spectrometric detection, a TurboIonSpray (ESI) source was operated in negative ion mode with a needle voltage of -4000 V. Chemical structures of FT, 5-FU and 5-CU, and optimized MS/MS parameters are summarized in Table 1.

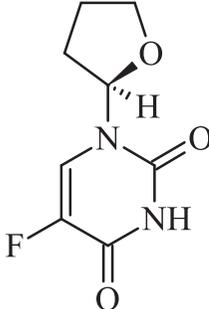
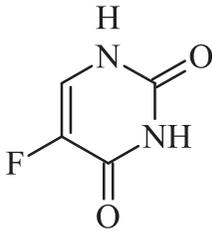
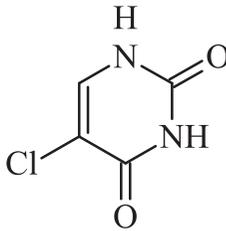
5. Statistical analysis

Age, height, body weight, body surface area, serum creatinine, initial and total doses, relative dose intensity, and treatment period were assessed using the Mann-Whitney *U* test. Sex differences were assessed using Fisher's exact probability test. Tear volumes between groups (during the administration period and washout period) were compared using the Mann-Whitney *U* test with Bonferroni correction. A two-tailed *p*-value < 0.05 was considered statistically significant.

6. Ethical considerations

This clinical study was performed according to the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" of the Aichi Cancer Center Ethical Committee (registration No. 2015-1-021). All patients in this study were explained to understand the purpose of the study and rights not to be compelled to participate into the study. A written informed consent was obtained from all the patients involved.

Table 1 Chemical structures and optimized MS / MS parameters

Compound	tegafur	5-fluorouracil	5-chlorouracil
Abbreviation	FT	5-FU	5-CU
Structure			
Chemical formula	C ₈ H ₉ FN ₂ O ₃	C ₄ H ₃ FN ₂ O ₂	C ₄ H ₃ ClN ₂ O ₂
Molar mass	200.17	130.08	146.53
Exact mass	200.06	130.02	145.99
Q1 (m/z)	199.7	128.9	144.8
Q3 (m/z)	42.0	41.9	42.0
Declustering potential (V)	-50	-40	-51
Entrance potential (V)	-10	-10	-10
Collision energy (eV)	-30	-30	-29
Cell exit potential (V)	-6	-5	-5
logD (pH8.0)	-0.90	-2.11	-1.90

RESULTS

1. Patient background

No significant differences were observed between groups in terms of patient background or treatment period (Table 2).

As shown in Fig. 1, the tear volume in the watering eyes group (median = 18.0 μ L) was significantly greater than that in the no watering eyes group (median = 13.0 μ L).

2. Quantification of FT and 5-FU by LC-MS/MS

Fig. 2 shows a typical LC-MS/MS chromatogram of standard compounds and a sample of patient's tears. The retention times of standard FT, 5-FU, and 5-CU were 6.28–6.30 min, 8.57–8.67 min, 7.66–7.67 min, respectively.

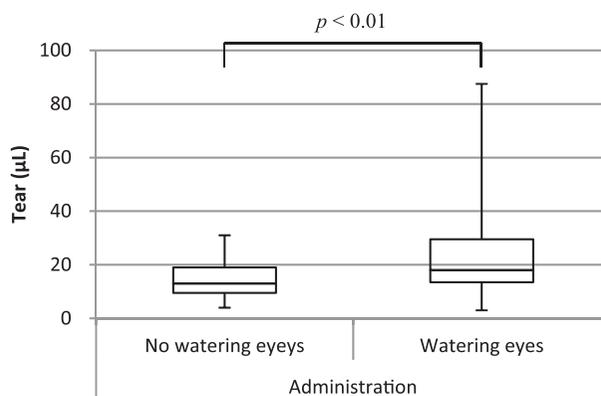
The linearity of FT and 5-FU was observed in a range from 1–1000 ng/mL (FT: $y = 0.115x + 0.0000037$, $r = 0.967$; 5-FU: $y = 1.01x + 0.0136$, $r = 0.998$). The detection and quantitation limits of FT were 4.95 ng/mL and 14.9 ng/mL, respectively; for 5-FU, they were 2.77 ng/mL and 8.31 ng/mL ($n = 4$). The yields (average \pm SE) of FT, 5-FU and 5-CU from the strip were 91.1 \pm 5.37%, 73.3 \pm 0.815 % and 55.0 \pm 0.957 % ($n = 4$), respectively.

Table 2 Patient characteristics

	Watering eyes (n=6)		No watering eyes (n=5)		<i>p</i>
	Median	(Range)	Median	(Range)	
Age (year)	70	(44–80)	63	(43–67)	0.297 ^a
Sex (male/female)	6	(3/3)	5	(3/2)	1.000 ^b
Height (cm)	156.15	(147.0–178.0)	156.2	(154.3–164.0)	0.535 ^a
Body weight (kg)	46.75	(40.0–58.8)	47.6	(31.2–78.4)	0.548 ^a
Body surface area (m ²)	1.372	(1.29–1.69)	1.404	(1.16–1.79)	0.548 ^a
Serum creatinine (mg/dL)	0.61	(0.43–0.98)	0.6	(0.47–0.8)	0.575 ^a
Initial dose (mg)	100	(80–120)	100	(80–120)	0.535 ^a
Total dose (mg)	13,440	(4,880–19,790)	13,440	(5,820–22,360)	0.548 ^a
Relative dose intensity (%)	85.13	(49.11–99.41)	79.95	(54.34–95.14)	0.522 ^a
Treatment period (course)	6.5	(2–8)	8	(2–8)	0.382 ^a
Treatment period (days)	319	(84–350)	350	(91–371)	0.601 ^a

Relative dose intensity = actual dose (mg) / standard dose (mg)

^a Mann-Whitney *U*-test, ^b Fisher exact probability

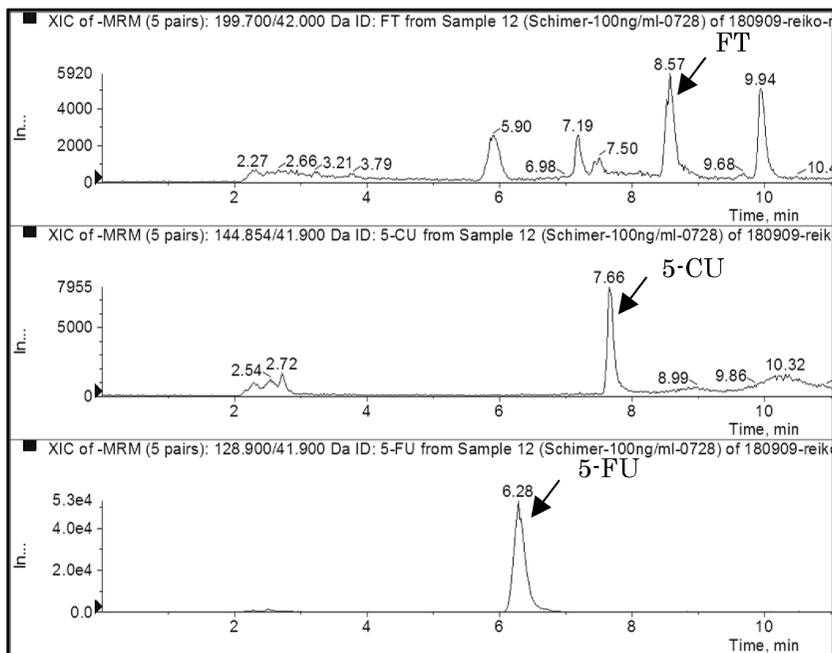
**Fig. 1** Comparison of tear volume between the no watering eyes and watering eyes groups

The line in the box-and-whisker plot indicates the median. The upper and lower edges of the box indicate the third and first quartiles, respectively, and the upper and lower edges of the whisker indicate the maximum and minimum values.

3. Changes in tear volume and FT and 5-FU levels in tears

Fig. 3 shows the changes in tear volume and FT and 5-FU levels in tears in two typical patients (case 1 and case 2) who underwent eight cycles of S-1 administration. Both cases were followed up from initiation until termination of treatment (48 weeks). Regardless of absence (case 1) or presence (case 2) of watering eyes, FT and 5-FU were detected in the tears during S-1 administration (day 14 and day 28). However, after the washout period (day 0), neither FT nor 5-FU were detected.

a



b

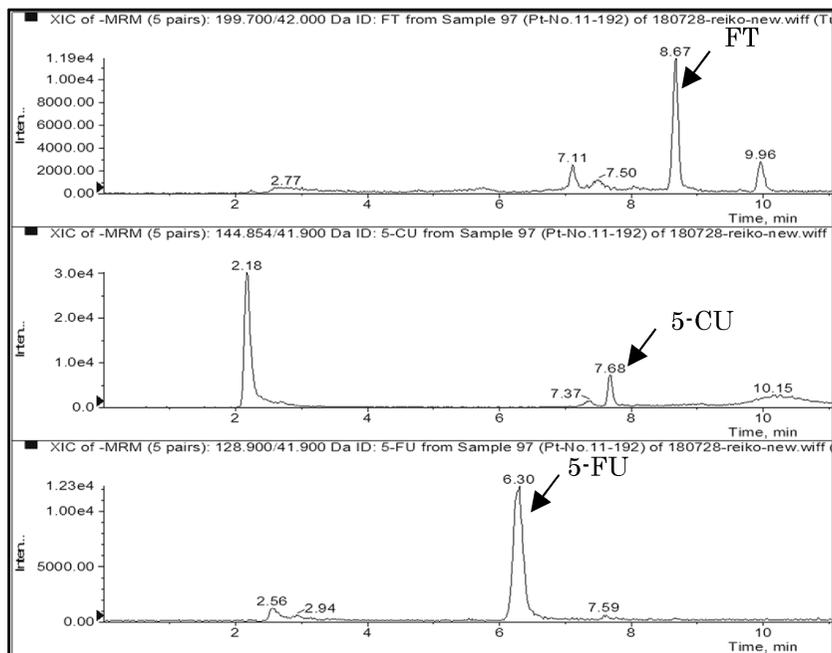
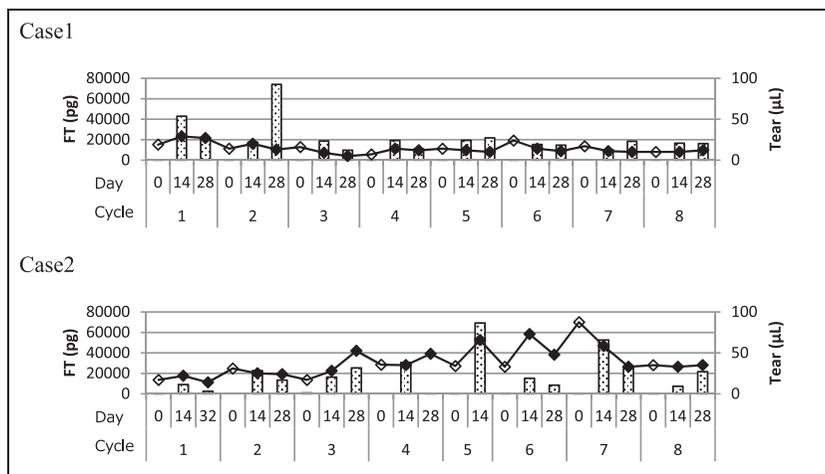


Fig. 2 LC-MS/MS analysis of FT and 5-FU in the tears of patients with long-term S-1 use. Chromatograms of a) standard compounds and b) FT and 5-FU in patient tears. Standard (5000 pg each FT and 5-FU, 500 pg 5-CU) or tears were applied to a Schirmer's test strip, extracted into distilled water, and dried. The residue was dissolved in 50 μ L 50% methanol. Five μ L of the sample was analyzed by LC-MS/MS (API 4000). FT: tegafur, 5-FU: 5-fluorouracil, 5-CU: 5-chlorouracil (internal standard)

Tegafur level in tears and S-1 usage

a



b

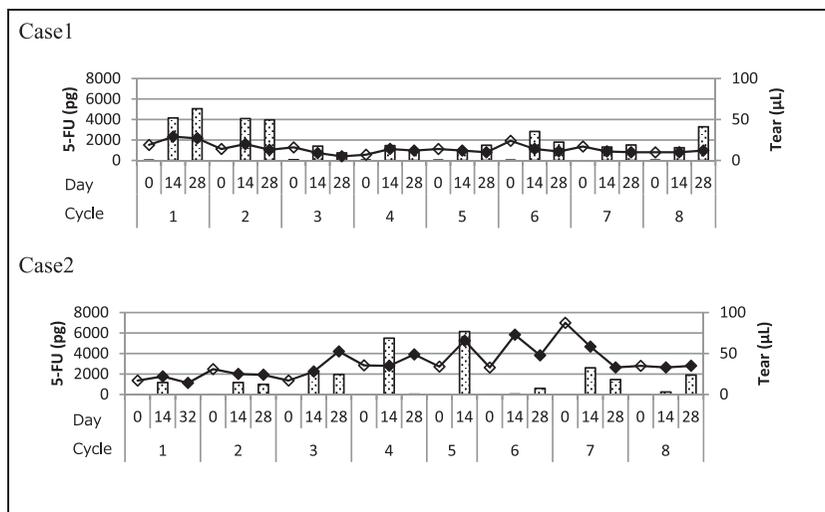


Fig. 3 Changes in tear volume and FT and 5-FU levels in the tears of two patients with long-term S-1 use

Changes in a) tear volume and FT level (pg) in tears and b) tear volume and 5-FU level (pg) in tears.

◆ : during S-1 administration ◇ : prior to S-1 administration or after washout

The line graph shows tear volume (μL) and the bar graph shows FT or 5-FU levels (pg) in tears. Case 1 is a patient with no watering eyes and case 2 is a patient with watering eyes.

Fig. 4 shows the median FT and 5-FU levels (ng/mL or pg) in the tears of all patients examined. As described above, FT and 5-FU rapidly disappeared from tears after taking a drug holiday in both the watering eyes and no watering eyes groups. FT and 5-FU levels (ng/mL) during S-1 administration tended to be lower in the watering eyes group than in the no watering eyes group likely due to dilution effect by excess tears (Fig. 4a, b). FT and 5-FU levels (pg) during S-1 administration did not differ between the two groups (Fig. 4c, d).

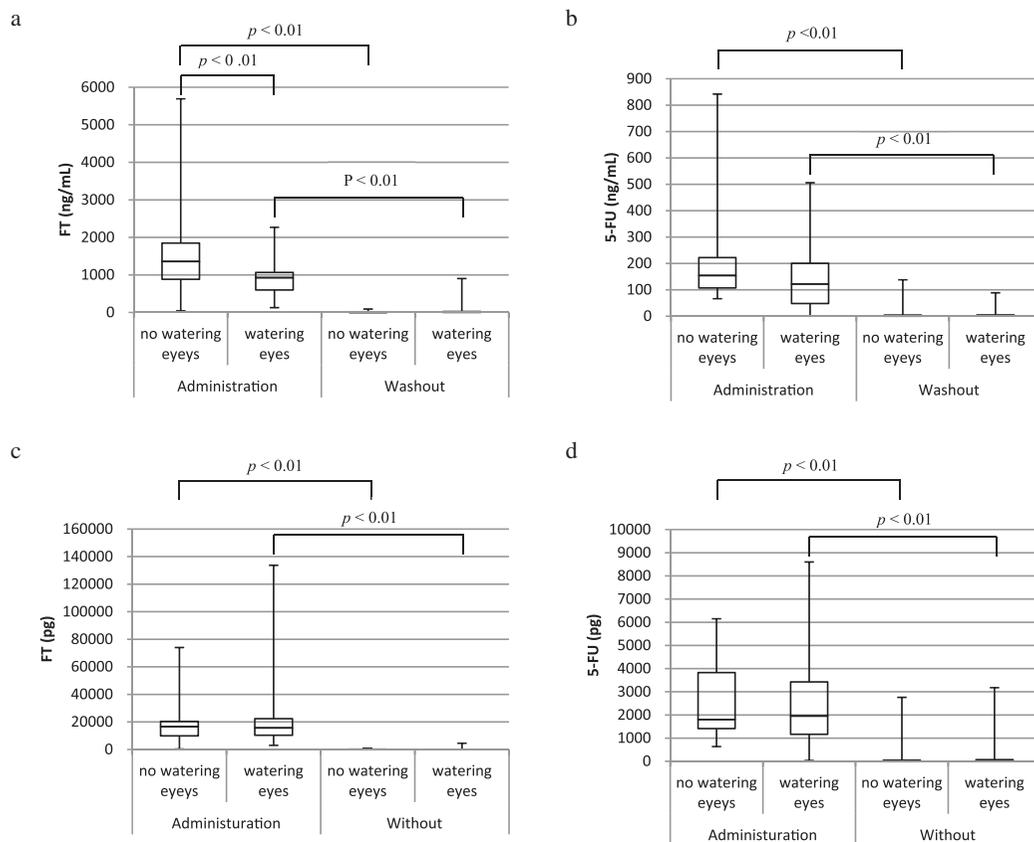


Fig. 4 Changes in FT and 5-FU levels in tears during long-term administration of S-1. Patients were separated into no watering eyes (6 patients) and watering eyes (5 patients) groups. “Administration” indicates combined results of FT or 5-FU levels collected during S-1 administration (day 14 and day 28 at a maximum of 8 cycles). “Washout” indicates combined results of FT or 5-FU levels prior to initiation of S-1 treatment or after 1 or 2 weeks of drug holiday (day 0), as shown in Fig.3.

The line in the box-and-whisker plot indicates the median. The upper and lower edges of the box indicate the third and first quartiles, respectively, and the upper and lower edges of the whisker indicate the maximum and minimum values.

a) FT level (ng/mL) in tears and b) 5-FU level (ng/mL) in tears.

c) FT level (pg) in tears and d) 5-FU level (pg) in tears.

4. Relationship of tear volume with FT and 5-FU levels in tears

Because there were no differences in FT and 5-FU levels between the watering eyes and no watering eyes groups (Fig. 4), they were combined for the analysis to examine the relationship between tear volume and FT and 5-FU levels in tears during S-1 administration. As shown in Fig. 5a, b, in the comparison using the concentration (ng/mL) of the compounds, no correlation was found. However, using the amount (pg) of compounds on the strip, a positive correlation was observed between tear volume and FT level ($r^2 = 0.471$) (Fig. 5c); however, there was still no correlation between tear volume and 5-FU level (pg) (Fig. 5d).

Tegafur level in tears and S-1 usage

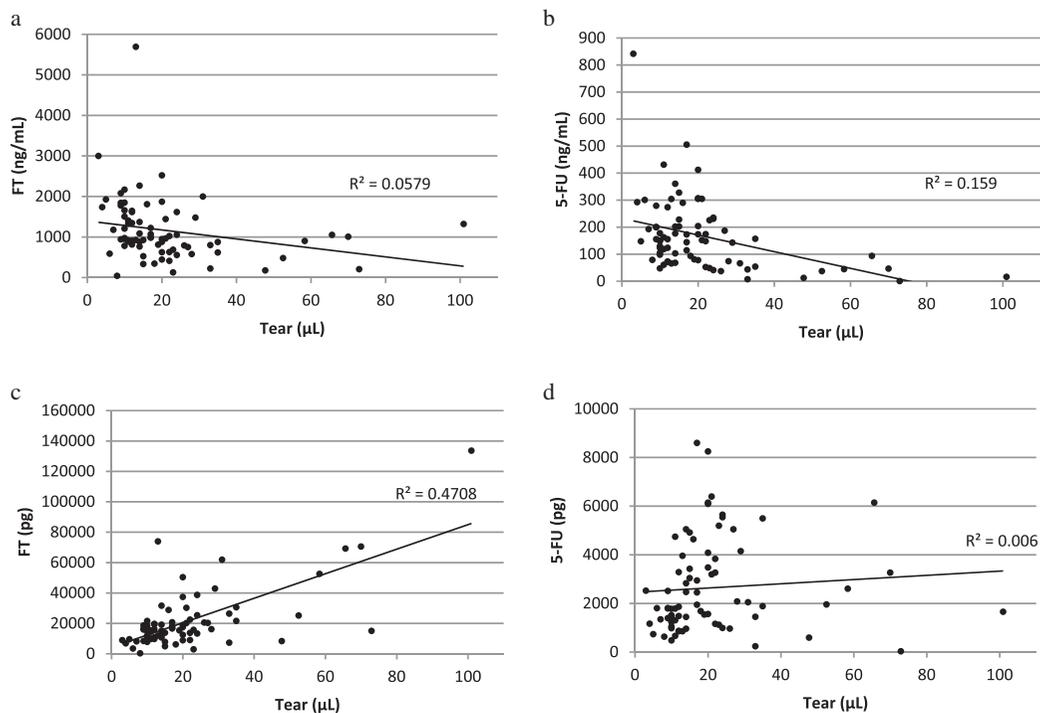


Fig. 5 Relationship between tear volume and FT and 5-FU levels in the tears of patients with S-1 use. Relationship a) between tear volume and FT level (ng/mL) and b) between tear volume and 5-FU level (ng/mL). Relationship c) between tear volume and FT level (pg) and d) between tear volume and 5-FU level (pg). Data from both groups (no watering eyes and watering eyes) were plotted. The solid line shows the correlation.

DISCUSSION

The present study investigated eye problems—especially watering eyes—and FT and 5-FU levels in the tears of patients receiving long-term S-1 monotherapy as adjuvant chemotherapy after gastric cancer surgery. Patients were principally treated with S-1 according to the standard protocol (4 weeks of administration followed by 2 weeks of washout) and underwent Schirmer's test on each consultation day before initiation of treatment until termination of treatment. The strips were used to measure tear volume and to collect tear samples for LC-MS/MS. This method offered high sensitivity for accurately measuring as little as 14.9 ng/mL FT and 8.31 ng/mL 5-FU in tears.

We found a relationship between tear volume and FT level (pg) in tears, but no relationship between tear volume and 5-FU level (pg). This observation was unexpected, as Kim et al previously reported that 5-FU level in blood during the steady-state trough was associated with eye problems during S-1 administration.¹⁴ Although there is no detailed information about the amount or time for 5-FU to translocate from blood to tears, our results coincide with the relative absence of eye problems in 5-FU monotherapy patients. This result suggests that 5-FU levels have little contribution, if any, to eye disorders, and that eye problems like watering eyes might be related to FT level (pg) instead. In our study, there was no correlation between tear volume and FT level when expressed as a concentration (ng/mL). One possible explanation is that a stimulant induces excessive tears when its concentration exceeds a certain threshold value, and

the excessive tears then lead to a reduced concentration of the stimulant by dilution. However, the actual reason for this finding remains to be elucidated.

Although predicting the incidence of eye problems is currently difficult, informing patients about adverse eye effects and sharing information among health care workers may help reduce exacerbation of such problems. Patient education should be an area of focus so that adverse eye reactions, such as watering eyes, are not overlooked or treated incorrectly.

The present study confirmed that FT and its active metabolite 5-FU are present in the tears of patients with long-term use of S-1, and suggested a relationship between FT level in tears and tear volume. Because, to the best of our knowledge, the combination anticancer drug UFT (FT - uracil) is not associated with eye problems, watering eyes might be a unique adverse effect of S-1. Thus, it is possible that gimeracil or oteracil, the other ingredients in S-1, may play some pathological role in inducing eye problem.²¹ Currently, we are undertaking a study to measure these components in the tears of patients undergoing S-1 treatment.

CONCLUSION

In patients receiving S-1 treatment, it is essential to prevent eye problems like excessive watering. The present study showed that FT and 5-FU levels in tears changed with administration of S-1. FT level (pg) in tears and tear volume were positively correlated, suggesting that watering eyes may be linked to FT level in tears.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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