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NOTE

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Safety of alternate-day treatment with TS-1™ (tegafur/gimeracil/oteracil) in tumor-bearing dogs: a pilot study

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ABSTRACT. Tegafur is a prodrug of fluoropyrimidine 5-fluorouracil (5-FU), while TS-1™ is an oral fixed-dose combination of three active drugs, tegafur, gimeracil, and oteracil. This pilot study evaluated the safety of tegafur/gimeracil/oteracil in the treatment of cancers in dogs. Tegafur/gimeracil/oteracil was administered orally at a mean dose of 1.1 mg/kg twice daily on alternate days, Monday-Wednesday-Friday, every week to 11 dogs with tumors. Partial response and stable disease were observed in one dog each, whereas six exhibited progressive disease. Three dogs were not assessed. Adverse events, the most serious being grade 2, were noted in seven dogs. Adverse events were acceptable, and the drug was effective in some dogs. Therefore, tegafur/gimeracil/oteracil may be useful for treating malignant solid tumors in canines.

KEY WORDS: dog, 5-fluorouracil, TS-1, Teysuno, tumor

Fluoropyrimidine 5-fluorouracil (5-FU) was first synthesized in the mid-1950s [26]. Currently, 5-FU is one of the most widely used anticancer agents, showing activity across a broad range of solid tumors, including gastrointestinal (GI) malignancies, breast cancer, head and neck cancer, and ovarian carcinomas in humans [26]. A few studies have reported the successful use of topical 5-FU in veterinary oncology [2, 18]; however, systemic 5-FU is rarely used in the management of epithelial tumors (hepatic, pancreatic, renal, and mammary) [5]. Accidental 5-FU ingestion has been associated with the development of toxicosis [3, 4, 9, 22]. 5-FU can cause dose-dependent myelosuppression, GI toxicity, and neurotoxicity in dogs and is contraindicated in cats owing to severe central nervous system toxicity [5]. Recently, 5-FU was used with carboplatin (CBDCA) for carcinomas in dogs, and this combination was effective and well-tolerated [16].

Tegafur is a prodrug of 5-FU [15, 27]. TS-1™ is an oral fixed-dose combination of three active drugs, tegafur, gimeracil, and oteracil [7, 10]. After absorption, tegafur is converted to 5-FU; gimeracil is a dihydropyrimidine dehydrogenase inhibitor that prevents the degradation of 5-FU [15]; oteracil, an orotate phosphoribosyltransferase inhibitor, decreases the activity of 5-FU in the gut to minimize its toxicity to the normal GI mucosa [15]. This combination was developed in Japan and sold under the brand name TS-1™. It was launched in Europe under the name Teysuno™ in 2011 [11].

The toxicity of tegafur/gimeracil/oteracil has been extensively studied in healthy beagle dogs [7, 10]. Tegafur/gimeracil/oteracil is primarily toxic to the eyes, lymphatic tissues, and reproductive organs, and death occurs owing to physiological deterioration and immunological dysfunction [7].

Tegafur/gimeracil/oteracil has been approved for the treatment of gastric, head and neck, colorectal, non-small cell lung, breast, pancreatic, and biliary tract cancers in humans [24]. It has been speculated to be a viable treatment option for solid tumors in dogs; however, its safety in dogs is not yet known.

We hypothesized that the combination of tegafur/gimeracil/oteracil could be safely administered to dogs with solid tumors. Therefore, this pilot study aimed to evaluate the safety of tegafur/gimeracil/oteracil in tumor-bearing dogs.

The dogs included in this pilot study were brought to the Azabu University Veterinary Teaching Hospital between October 2014 and March 2020. All procedures were performed in accordance with the guidelines approved by the Azabu University Animal

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Table 1. Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE, ≤grade 3)

	Grade		
	1	2	3
Conjunctivitis/ocular surface disease	Asymptomatic or minimally symptomatic; however, not interfering with the function	Symptomatic, significant discharge; interfering with function but not ADL; topical antibiotics or other topical intervention indicated	Symptomatic and interfering with ADL, operative intervention indicated
Keratitis (corneal inflammation/ corneal ulceration)	Abnormal ophthalmologic changes only, intervention not indicated	Symptomatic and interfering with function, but not ADL	Symptomatic and interfering with ADL, operative intervention indicated
Anorexia	Coaxing or dietary change required to maintain appetite	Oral intake altered (≤3 days) without significant weight loss; oral nutritional supplements/appetite stimulants may be indicated	Of >3 days duration; associated with significant weight loss (≥10%) or malnutrition; IV fluids, tube feeding, or force-feeding indicated
Diarrhea	Increase of up to two stools per day over baseline; no increase in frequency; however, consistency decreased over baseline	Increase of 3–6 stools per day over baseline; medications indicated; parenteral (IV or SC) fluids indicated ≤48 hr; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence >48 hr; IV fluids >48 hr; hospitalization; interfering with ADL
Hyperpigmentation (Dermatologic)	Slight or localized	Marked or generalized	
Bilirubin	>ULN to 1.5× ULN	>1.5 −3.0 × ULN	>3.0–10 × ULN

ADL: activities of daily living (eating, sleeping, defecating, and urinating), ULN: upper limit of normal.

Experimentation Committee (No. 141001-2). Regarding ethics, it was implemented under the best practice recommendation as much as possible [20]. Additionally, we retained the inclusion and exclusion criteria and written informed consent was obtained from the owners of the animals. The inclusion criteria were that the animals had undergone prior tumor removal or irradiation for solid malignant tumors and had tumor relapse. The exclusion criteria were the presence of the best practice option that has already been established and could predict the effect of a treatment such as chemotherapy, surgery, and irradiation. Prior to treatment with tegafur/gimeracil/oteracil, the anticancer drugs administered were CBDCA (Paraplatin™, Bristol-Myers Squibb K.K., Tokyo, Japan, n=7), toceranib (Palladia™, Zoetis Japan Inc., Tokyo, Japan, n=2), and metronomic cyclophosphamide (Endoxan™, Shionogi & Co., Ltd., Osaka, Japan, n=1).

Hypofractionated radiotherapy was performed in certain cases (n=6). Acridine orange photodynamic therapy and cribriform irradiation were performed in three dogs [12–14]. The dogs included in this study were administered tegafur/gimeracil/oteracil (TS-1™, Thaiho Pharmaceutical Co., Ltd., Tokyo, Japan) as an adjuvant. Data on the breed, sex, age, body weight, diagnosis, treatment history, TNM classification at the initiation of tegafur/gimeracil/oteracil therapy, dose, administration period, cause of discontinuation, concomitant anticancer drug administration, tumor response, and adverse events were obtained from the medical records. Drugs were prescribed at 2–4-week intervals for each dog.

The TNM staging, tumor response, and adverse events were recorded according to the World Health Organization classification [19], canine response evaluation criteria in solid tumors (cRECIST) [17], and veterinary cooperative oncology group–common terminology criteria for adverse events (VCOG-CTCAE, Table 1) [25] was not assessed; only clinical responses (response, progression) were evaluated by the cRECIST assessment in some dogs owing to a lack of imaging.

A study on the toxicity of tegafur/gimeracil/oteracil in beagle dogs demonstrated considerable mortality when a dose of 2.5–3.0 mg/kg was administered once daily, while a dose of 1 mg/kg was found to be safe [7, 10]. This drug had a narrow safety margin, and the upper limit was 2.5 mg/kg/day. While twice-daily (BID) dosing is used in humans, an alternate-day dosing schedule of 5-FU may be a better regimen in dogs owing to its strong time-dependent mode of action [1, 21, 24]. There were no safety data for beagle dogs, and tegafur/gimeracil/oteracil was administered orally at a dose of 2−3 mg/kg divided BID on alternate days, Monday-Wednesday-Friday (M-W-F), every week to dogs with solid tumors.

This study included 11 dogs with malignant solid tumors, and the cohort characteristics are summarized in Table 2. The mean age was 11.8 ± 2.5 (range: 9–16) years, and the bodyweight (mean ± SD) was 10.7 ± 6.8 (range: 4.5–27.0) kg. The diagnosis, treatment history, and TNM classification at the initiation of therapy are summarized in Table 2, while the treatments, response, and adverse events are summarized in Table 3. A mean dose of 1.1 ± 0.3 mg/kg tegafur/gimeracil/oteracil BID was administered orally on alternate days (M-W-F) every week. The dose was reduced to half in one dog (case number 3) a month later owing to anorexia related to olfactory loss.

The median duration of tegafur/gimeracil/oteracil administration was 104 days (range: 14–460 days). The causes of discontinuation were tumor progression (n=6) and worsened quality of life due to adverse events (n=3). The treatment of the two dogs was ongoing during the writing of this manuscript. The anticancer agent CBDCA was co-administered with tegafur/gimeracil/oteracil to three dogs (n=3) for one, five, and 20 treatment cycles, respectively. Partial response (PR, case number 5, Fig. 1), stable disease (SD, case number 4), and progressive disease (PD) were observed in one, one, and six dogs, respectively, whereas three were not assessed (NA). Of the three dogs that were not assessed, seizures were controlled for 49 days in one dog (case number

Table 2. Summary of cohort characteristics

	Breed	Sex	Age (year)	Body weight (kg)	Diagnosis	Hx-Surgery	Hx-RT	Hx-chemotherapy*	TNM classification
1	Cairn Terrier	MI	10	6.1	Tonsil SCC		4 months ago, 28 Gy/4 fract	Low CBDCA (2) metronomic chemotherapy	T3bN3M0
2	Labrador Retriever	MI	15	27	Intranasal TCC	AO-PDT (37 months ago)	36 months ago, 28 Gy/4 fract	Low CBDCA (5)	T3N0M0
3	Dachshund	MI	11	7.3	ASAGACA	Obstruction of enlarged sub-lumber LN 2 months ago		Low CBDCA (3)	T0N0M1
4	Cocker Spaniel	FS	11	9.8	ASAGACA	14 months ago		Low CBDCA (14)	T2N1bM0
5	Boston Terrier	FI	10	8.5	Malignant mixed tumor of mammary gland	12 months ago		Low CBDCA (5)	T3N1M1
6	Dachshund	MC	14	4.5	OMM	5 months ago	4 months ago, 22 Gy/4 fract	Low CBDCA (4)	T3bN1bM1
7	Mixed breed	FS	16	9.6	IMC	1 month ago			T4N1M1
8	Cocker Spaniel	MI	10	14	ASAGACA	9 months ago		Low CBDCA (10)	T0N1M0
9	West Highland White Terrier	MC	9	8.3	Intranasal AC	AO-PDT (23 months ago)	22 months ago, 43 Gy/15 fract	Low CBDCA (12)	T3N1M0
10	Mix	MC	12	20.7	Intranasal TCC	AO-PDT (3 months ago)	4 months ago, 44 Gy/11 fract	Toceranib	T1N0M0
11	Toy Poodle	MI	12	5.0	Intranasal AC		3 years ago, 30 Gy/4 fract, Re-RT (4 months ago, 15 Gy/2 fract), re-RT (1 month ago, 12 Gy/2 fract)	Toceranib, and low CBDCA (3)	T3N0M0

*The number in parentheses shows the number of CBDCA administrations. AC: adenocarcinoma, AO-PDT: acridine orange photodynamic therapy and cribriform irradiation, ASAGACA: anal sac apocrine grand adenocarcinoma, FI: female intact, FS: female spayed, Hx: history, IMC: inflammatory mammary carcinoma, LN: lymph node, MC: male castrated, MI: male intact, OMM: oral malignant melanoma, RT: radiotherapy, SCC: squamous cell carcinoma, Sx: surgery, TCC: transitional cell carcinoma, low CBDCA: low-dose carboplatin, 100–120 mg/m^2 (treatment number).

Table 3. Summary of treatments, response, and adverse events

	Dose* (mg/kg)	Concomitant treatment**	Administration period (days)	cRECIST response (days)	Clinical response (days)	Classification of discontinuation	Adverse events (grade)
1	1.64	-	14	NA	Progress	TP	-
2	0.74	-	21	PD	-	AE	Anorexia (2)
3	1.37	CBDCA (20)	544	PD	-	TP	ScP (1), CoP (1), anorexia ROL (2)
4	1.02	CBDCA (5)	141	SD (56)	-	AE	Diarrhea (1), ScP (1), SkP (1), increased t-Bil (1)
5	1.18	-	207	PR (147)	-	AE	ScP (2), CoP (1), anorexia ROL (2)
6	1.11	-	74	PD	-	TP	-
7	1.05	-	60	PD	-	TP	-
8	1.43	CBDCA (1)	52	PD	-	TP	-
9	0.96	-	249	NA	Response (49)***	TP	ScP (1), SkP (2)
10	0.97	-	322<	PD			ScP (1)
11	1.00	-	182<	NA	Response (120)		ScP (2), CoP (2), SkP (1)

*Tegafur/gimeracil/oteracil was administered twice-daily (BID) on alternate days, Monday-Wednesday-Friday (M-W-F) weekly, **The number in parentheses shows the administration number of CBDCA, *** seizure controlled for 49 days (n=1). AE: adverse event, CoP: corneal pigmentation, CBDCA: carboplatin, NA: not assessed, cRECIST: canine response evaluation criteria in solid tumors, PD: progressive disease, PR: partial response, ROL: related to olfactory loss, ScP: scleral pigmentation, SD: stable disease, SkP: skin pigmentation, TP: tumor progression.

9) and nasal symptoms were controlled for 4 months in another dog (case number 11), which is suggestive of clinical response (Table 3). Therefore, the efficacy of tegafur/gimeracil/oteracil was confirmed and suggested in two dogs each.

Adverse events, most of which were observed after a period of 2 months, were noted in seven dogs (Table 3). Adverse events

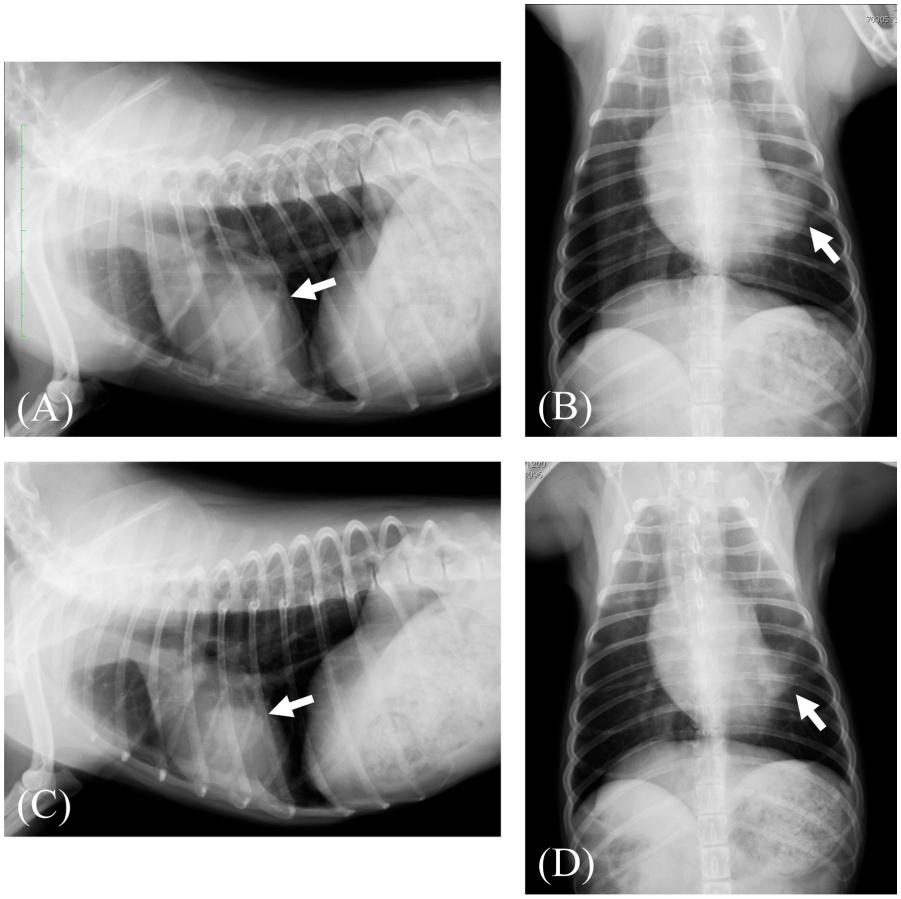

Fig. 1. Thoracic radiographs of a dog with partial response (PR; case number 5). Response in the lung metastasis (white allow) from the malignant mixed tumor of the mammary gland 147 days after tegafur/gimeracil/oteracil therapy initiation. Above (A, B) and below (C, D): before and 147 days after tegafur/gimeracil/oteracil therapy initiation, respectively.

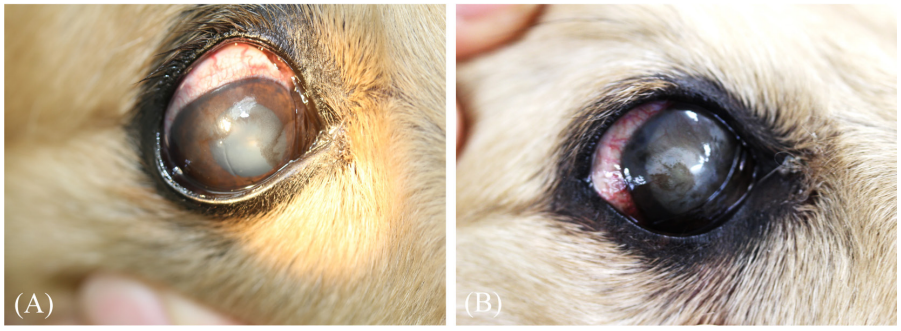

Fig. 2. Scleritis and keratic pigmentation in case number 3. The keratic pigmentation was observed. Left (A) and right (B): 30 and 479 days after tegafur/gimeracil/oteracil therapy initiation, respectively.

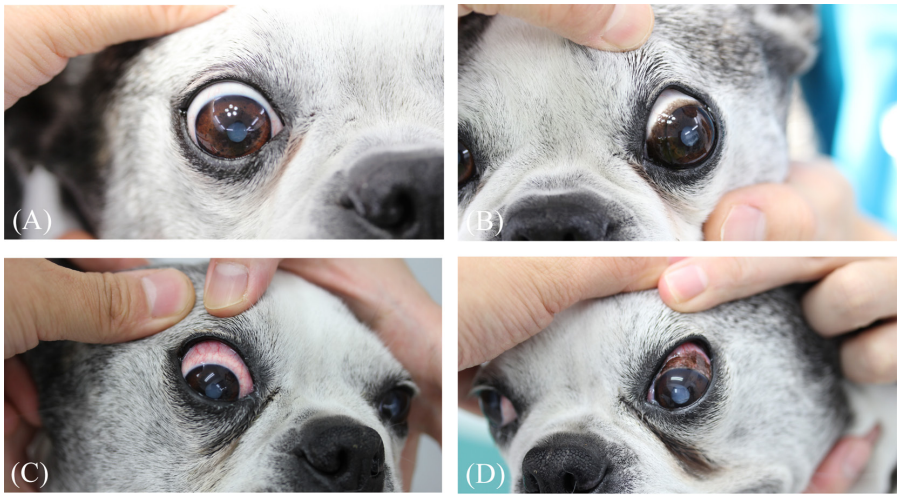

Fig. 3. Scleritis in both the eyes of the dog (case number 5). Scleral pigmentation was observed in the left eye. Above (A, B) and below (C, D): 40 and 210 days after tegafur/gimeracil/oteracil therapy initiation, respectively.

included scleral pigmentation (n=6), corneal pigmentation (n=2), skin pigmentation (n=3), anorexia related to olfactory loss (n=2), diarrhea (n=1), and increased total bilirubin (t-Bil, n=1). Scleral and corneal pigmentation were classified as conjunctivitis/ocular surface disease and keratitis (corneal inflammation/corneal ulceration), respectively (Table 1, Figs. 2 and 3).

A majority of the adverse events observed were grade 2 (anorexia [n=3], scleral pigmentation [n=2], corneal pigmentation [n=1], and skin pigmentation [n=1]). In dogs with PD, tegafur/gimeracil/oteracil was discontinued after the onset of anorexia (grade 2) in three cases and increased t-Bil (grade 1) in one case. The adverse events resolved after treatment discontinuation and the drug was resumed in only one dog (case number 3) at half the dose (0.7 mg/kg) for 460 days.

The findings of this pilot study demonstrated the safety of orally administered tegafur/gimeracil/oteracil to 11 dogs with solid tumors, at a mean dose of 1.1 mg/kg BID on alternate days (M-W-F) a week. Adverse events included eye, skin, GI, and neurological abnormalities. Most adverse events were acceptable, and most adverse events were grade 2. Although most dogs had advanced-stage tumors, tegafur/gimeracil/oteracil was successfully administered for a median of 104 days. Efficacy was confirmed in two of the 11 dogs (numbers 4 and 5) and was suggested in two dogs (numbers 9 and 11).

The reported adverse events of tegafur/gimeracil/oteracil in healthy beagle dogs include scleral pigmentation; corneal opacity; mucositis (oral, nasal, and ocular); GI symptoms (anorexia, salivation, vomiting, diarrhea, and hematochezia); and lethargy [7, 10]. There was no severe myelosuppression or neurological abnormalities associated with 5-FU. In this pilot study, tegafur/gimeracil/oteracil was administered orally for a median duration of >3 months. Several adverse events, such as those affecting the eyes, GI tract, and skin, were noted in the present cohort; however, there were no grade 3 adverse events. Adverse effects on the eyes and skin were acceptable and did not warrant discontinuation of the drug; however, most dogs exposed to long-term administration of the drug exhibited scleral pigmentation. Recent studies have suggested the alleviating effect of artificial-tear instillation on the corneal-surface damage induced by tegafur/gimeracil/oteracil in dogs [8]. In contrast, even in grade 1 and 2 adverse events such as gastric abnormality of anorexia (grade 2), increased t-Bil (grade 1), and neurologic abnormality of anorexia related to olfactory loss, owners wanted to discontinue tegafur/gimeracil/oteracil administration. Therefore, the dose did not increase. The dose of tegafur/gimeracil/oteracil administered in this study may be tolerated in dogs with malignant solid tumors.

This pilot study had some limitations. First, the condition of animals, the tumor types and stages in this cohort were heterogeneous, and previous and concomitant treatments were not similar for all dogs. Second, the treatment period was short in some cases, and the sample size was small. Therefore, an objective analysis of efficacy could not be performed. Third, the drug dose was not increased using a 3 + 3 dose-escalation design [6]. However, the lethal dose of this drug is already known to be 2.5–3.0 mg/kg SID [7, 10]. Fourth, concomitant low-dose carboplatin was administered to three dogs using a low-dose chemotherapy protocol [23]. These cases may have affected the outcome of this study, particularly in case 4.

In conclusion, the findings of this pilot study indicate that tegafur/gimeracil/oteracil at a dose of 1.1 mg/kg BID on alternate days a week might be tolerated for treating tumors in dogs. The adverse events in this cohort were acceptable, and the drug was effective in some dogs. Therefore, this drug may be a feasible treatment option for malignant solid tumors. Further studies on tegafur/gimeracil/oteracil alone or in combination with other drugs with larger sample sizes are needed to validate our findings.

CONFLICT OF INTEREST. The authors declare that they have no conflicts of interest.

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