Received: 24 March 2023 | Revised: 31 October 2023 | Accepted: 20 November 2023

DOI: 10.1111/vco.12945

ORIGINAL ARTICLE

Veterinary and Comparative Oncology WILEY

Spotlight on capecitabine for the treatment of unresectable or metastatic carcinoma of various origin: A retrospective study of 25 dogs

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Abstract

Capecitabine, the oral prodrug of 5-fluorouracil, is indicated in people to treat various malignant epithelial cancers. In dogs, capecitabine has not been extensively evaluated. The aim of this retrospective study was to investigate toxicity and preliminary efficacy of single agent capecitabine in dogs with advanced malignant epithelial cancers of any site, for which no effective therapy existed, conventional treatment failed or was declined. Capecitabine was administered orally at 750 mg/m^2 from day 1 to 14, followed by 1-week rest period, given as 3-week cycles. Safety evaluation was performed after 2 cycles, and every 2–3 cycles thereafter. Tumour response was determined every 2–3 cycles. Twenty-five dogs with hepatocellular carcinoma ($n = 6$), lung papillary carcinoma ($n = 4$), anal sac adenocarcinoma ($n = 3$), colic adenocarcinoma ($n = 2$), and other individually represented epithelial cancers ($n = 10$) were included. Dogs received a median of 4 cycles (range, 2–43) for a median of 84 days (range, 42–913). Toxicity occurred in 17 (68.0%) dogs; the most frequent adverse events were gastrointestinal, with the majority being self-resolving and of mild grade. Of the 22 dogs with macroscopic disease, 3 (13.6%) achieved partial remission, 16 (72.7%) were stable and 3 (13.6%) progressed; overall clinical benefit rate was 86.4%. Median progression-free interval was 93 days (95% CI 42–154; range, 1–521) and median tumour-specific survival was 273 days (95% CI 116–482; range 45–913). These findings suggest that capecitabine is an attractive option for the treatment of several types of carcinomas in dogs. Prospective studies are warranted to optimize the scheduling of capecitabine and confirm its efficacy.

KEYWORDS
antimetabolite, canine, carcinoma, clinical benefit, oral chemotherapy, toxicity

1 | INTRODUCTION

Capecitabine is an orally administered nucleoside inhibitor, which is adsorbed by the intestinal mucosal membrane intact and is subsequently converted to its only active metabolite, 5-fluorouracil, selectively at the tumour site through a cascade of three enzymes. The lastly involved enzyme, thymidine phosphorylase, is present at higher levels in tumour cells compared with healthy tissue, thereby allowing for selective activation of the drug and reduction of systemic toxicity.[1,2]

Cytotoxicity of capecitabine results from the inclusion of the active drug into replicating RNA and from depletion of thymidine following binding with thymidylate synthase.[2]

In people, capecitabine is indicated for the treatment of various malignant epithelial cancers, including metastatic breast and colorectal carcinoma, either as single agent or in combination with a wide range of other cytotoxic agents.[3–5] The registered capecitabine dose is 1250 mg/m^2 twice daily for 2 weeks, with 1 week off.[6] Capecitabine-induced adverse events include hand-foot syndrome, gastrointestinal toxicity, hematologic toxicity and cardiotoxicity.[7,8] It is believed that capecitabine is the only cytotoxic agent without cumulative toxicity.[9] Also, due to its short half-life, quick dose adjustments can be made in case toxicity occurs.[10]

In dogs, capecitabine has not been extensively studied. It has been used as an immunosuppressive drug to prevent rejection of allografts in DEA-mismatched dogs. However, at the dose of 250 mg/m^2 twice daily, severe and unpredictable neurotoxicity and variable ocular toxicity occurred.[11–13]

Additionally, it has been used in a dog with liver metastasis from an intestinal liposarcoma at the dose of 750 mg/m^2 once daily for 2 weeks followed by 1 week rest, without any objective response.[14]

Dogs with locally advanced and/or metastatic carcinoma of various anatomic origin have limited treatment options and a dismal prognosis with poor quality of life.[15–18]

Given this background and the therapeutic index documented in human oncology patients, the aim of this retrospective study was to investigate toxicity and preliminary efficacy of single agent capecitabine in dogs with advanced malignant epithelial cancers.

2 | MATERIALS AND METHODS

2.1 | Population and inclusion criteria

Medical records were retrospectively reviewed from client-owned dogs that received capecitabine at the Veterinary Teaching Hospital of the University of Bologna between October 2018 and December 2022.

Dogs were considered eligible to receive capecitabine if they had a histologically confirmed carcinoma of any site, for which no effective therapy existed, conventional treatment failed or was declined by the owner.

Additionally, one or more of the following criteria were required: unresectable carcinoma, incompletely excised carcinoma with microscopic residual disease, high-grade carcinoma and/or presence of gross metastasis.

Dogs were included in the analysis if they had received at least two cycles of capecitabine.

Tumours were staged according to TNM guidelines at the start of capecitabine. Specific diagnostic methods depended on the anatomic site of the tumour. Carcinomas were either directly measured with callipers or imaged and measured using radiographic, ultrasonographic and/or tomographic techniques.

A baseline CBC, serum biochemistry and urinalysis were obtained before capecitabine administration. The dogs included in the analysis did not receive any concurrent antitumoral treatment; previous treatments were permitted and registered.

2.2 | Treatment protocol

Capecitabine was administered orally at the dose of 750 mg/m^2 from day 1 to day 14, followed by 1-week rest period, given as 3-week cycles.[14] The dose was administered to the nearest 150 mg.

Treatment was continued every 21 days until progressive disease (PD) was observed or toxicity occurred.

The study did not fall within the application areas of Italian Legislative Decree which governs the protection of animals used for scientific or educational purposes; therefore, ethical approval was waived for this study. All owners were informed of the advantages and disadvantages of the treatment options, including unknown treatment outcomes and treatment-related morbidities. The final treatment decision was made jointly by each owner and oncologist, with full respect for the option to decline participation.

Written owner informed consent was obtained.

2.3 | Toxicity evaluation

The entire population was assessed for toxicity. Dogs were evaluated by physical examination, CBC, serum biochemical profile and urinalysis after two cycles of capecitabine, and every 2–3 cycles thereafter.

Drug toxicity was monitored by the evaluation of laboratory data and information obtained from owners and graded according to the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (VCOG-CTCAE) v1.1.[19]

2.4 | Preliminary efficacy evaluation

Only dogs with measurable cancer were included in the portion of the study that evaluated efficacy.

Tumour response was determined at each examination, occurring every 2–3 cycles of capecitabine, by measuring tumours as previously described. To obtain data that were as objective as possible, the tumours were compared at various timepoints using the same imaging technique and operator.

According to RECIST criteria,[20] treatment response was categorized as follows: complete response (CR, resolution of all target and non-target lesions and absence of new lesions), partial response (PR, 30% or greater reduction in the longest diameter of target lesions, no progression of non-target lesions, and absence of new lesions), stable disease (SD, decrease in target lesions of less than 30% or increase of target lesions less than 20%, no progression of non-target lesions, and no new lesions), and PD (development of greater than 20% increase in target lesions, or documentation of new lesions).

All response categories were required to persist for at least 28 days. Decreases in tumour size for shorter durations were defined as SD.

Dogs were defined as experiencing clinical benefit (CB) if they obtained CR, PR or SD for at least 28 days.[21]

3 | STATISTICAL ANALYSIS

Retrieved data included signalment, histologic diagnosis, clinical stage based on imaging, clinico-pathologic findings, previous treatments, capecitabine dose and number of cycles, concurrent drugs, treatment-related toxicity and outcome.

Categorical variables were summarized as frequency (percentage), whereas numerical variables were summarized as median (range). Non-normality of numerical data was assessed using the Shapiro–Wilk test.

Duration of clinical benefit (CB) was defined as the time from starting capecitabine to PD, suspension of treatment due to onset of toxicity, or death. Progression-free interval (PFI) was defined as the interval between the initiation of capecitabine to the documentation of PD or suspension of treatment due to onset of toxicity. Tumour-specific survival (TSS) was calculated from the date of initiation of chemotherapy to the date of tumour-related death. For TSS analysis, dogs were censored if they were alive at the time of study closure or died for tumour-unrelated causes, whereas for PFI dogs were censored if, by the last examination, PD had not occurred or distant metastases had not developed.

Survival curves were generated according to the Kaplan–Meier product-limit method. Survival estimates are presented as medians with the corresponding 95% confidence intervals (CI). The influence of potential prognostic variables (nodal or distant metastasis at diagnosis, previous surgery and/or chemotherapy, and piroxicam administration) on CB, PFI and TSS was investigated with the log-rank test.

Data were analysed by use of commercial software programs (MedCalc® Statistical Software version 20.011, MedCalc Software Ltd, Ostend, Belgium). The significance level was set at $p < .05$.

4 | CELL LINE VALIDATION STATEMENT

No cell lines were used in the current study.

5 | RESULTS

5.1 | Dogs and tumour characteristics

Twenty-five dogs matched the inclusion criteria. There were 15 (60.0%) females (13 spayed) and 10 (40.0%) males (7 neutered). Median age was 126 months (range, 84–196) and median weight was 27 kg (range, 8–42). Breeds included 8 (32.0%) mixed breeds, 2 (8.0%) each of Labrador Retriever, Golden Retriever and Jack Russel Terrier, and one (4.0%) each of American Staffordshire terrier, Australian Shepard, Boxer, Bull Mastiff, Cane Corso, Dachshund, German Shepherd, Griffon Bleu, Pinscher, Samoiedo and Springer Spaniel.

Primary cancer histotypes and locations included hepatocellular carcinoma ($n = 6$; 24.0%), lung papillary carcinoma ($n = 4$; 16.0%), apocrine gland anal sac adenocarcinoma ($n = 3$; 12.0%), colic adenocarcinoma ($n = 2$; 8.0%), and one (4.0%) each of the following: colorectal carcinoma, mammary tubular adenocarcinoma, malignant mammary myoepithelioma, mammary inflammatory carcinoma, pancreatic exocrine carcinoma, ceruminous carcinoma, nasal carcinoma, renal carcinoma, thymic carcinoma and a carcinoma of unknown primary (Table 1).

Eighteen dogs (72.0%) received some form of treatment before being treated with capecitabine: 16 underwent surgery and 9 received chemotherapy. Among the latter, 3 received dose-intense chemotherapy (carboplatin, $n = 2$; 5-fluoruracil, $n = 1$), 2 toceranib, 2 toceranib and dose-intense chemotherapy (carboplatin and doxorubicin, respectively), and 2 were treated with metronomic therapy.

The median time between the last drug administration and the start of capecitabine was 14 days (range, 4–180).

At the start of capecitabine, 22 (88.0%) dogs had macroscopic disease (8 unresectable, 6 unresectable and metastatic, 8 metastatic), and 3 (12.0%) had a microscopically reduced, histologically aggressive carcinoma (including thymic carcinoma, mammary tubular adenocarcinoma and ceruminous carcinoma).

5.2 | Capecitabine treatment and tolerability

Median daily dose of capecitabine was 745 mg/m^2 (range, 630–778). Dogs received a median of four cycles (range, 2–43). Alongside, 9 (36.0%) dogs were also treated with oral piroxicam at the dose of 0.3 mg/kg daily, which was started before capecitabine with no documented antitumor efficacy. Median capecitabine treatment duration was 84 days (range, 42–913).

All dogs were evaluable for toxicity. Adverse events (AE) occurred in 17 (68.0%) dogs and consisted of grade 1 ($n = 8$) and grade 2 ($n = 4$) gastrointestinal side effects, grade 1 ($n = 1$) and grade 2 ($n = 2$) neurologic symptoms (consisting of 1 episode of afinalistic vocalizations and 2 isolated epileptic seizures, respectively), grade 1 ($n = 2$) neutropenia, grade 1 ($n = 2$) ocular toxicity and grade 1 ($n = 2$) dermatologic toxicity. Four out of 12 (33.3%)

TABLE 1 Tumour characteristics, staging results, previous treatments and outcomes in 25 dogs with carcinoma receiving capecitabine.

	Tumour site	Histotype	Tumour grade	Metastasis	Previous treatment	Treatment response	Duration of CB (days)	PFI (days)	TSS (days)
Case 1	Mammary gland	Tubular adenocarcinoma	2	Nodal	Sx and chemo	/	/	/	/
Case 2	Kidney	Renal carcinoma	/	Absent	/	SD	42	42	+337
Case 3	Liver	HCC	/	Absent	Chemo	SD	80	80	+166
Case 4	Liver	HCC	/	Absent	/	SD	55	55	56
Case 5	Lung	Papillary carcinoma	/	Distant and nodal	/	SD	42	42	64
Case 6	Mammary gland	Myoepithelioma	2	Distant	Sx	SD	37	37	47
Case 7	Lung	Papillary carcinoma	2	Nodal	Sx	SD	71	71	121
Case 8	Lung	Papillary carcinoma	2	Absent	Sx	SD	168	168	+325
Case 9	Ear canal	Ceruminous carcinoma	/	Nodal	Sx	/	/	/	/
Case 10	Nasal cavity	Nasal carcinoma	/	Absent	Chemo	PD	/	1	116
Case 11	Liver	HCC	/	Distant	Sx	SD	42	42	+913
Case 12	Pancreas	Exocrine carcinoma	/	Nodal	Sx and chemo	SD	102	102	280
Case 13	Anal sac	ASGC	/	Distant and nodal	Sx and chemo	SD	154	154	273
Case 14	Anal sac	ASGC	/	Nodal	Sx and chemo	SD	131	131	131
Case 15	Colon/rectum	Carcinoma	/	Nodal	/	PR	93	93	571
Case 16	Liver	HCC	/	Nodal	/	SD	64	64	236
Case 17	Liver	HCC	/	Absent	/	SD	129	129	617
Case 18	Thymus	Carcinoma	/	Distant	Sx	/	/	/	/
Case 19	Liver	HCC	/	Nodal	Sx	PR	+521	+521	+521
Case 20	Colon	Adenocarcinoma	/	Nodal	/	PR	+97	+97	+97
Case 21	Colon	Adenocarcinoma	/	Absent	Sx	SD	362	362	462
Case 22	Lung	Papillary carcinoma	1	Distant	Sx and chemo	PD	/	1	70
Case 23	Anal sac	ASGC	/	Nodal	Sx and chemo	SD	107	107	163
Case 24	Not known	CUP	/	Nodal	Sx and chemo	SD	53	53	415
Case 25	Mammary gland	Inflammatory carcinoma	3	Distant	Sx	PD	/	1	45

Abbreviations: ASGC, anal sac gland carcinoma; Chemo, chemotherapy; CUP, carcinoma of unknown primary, HCC, hepatocellular carcinoma; PFI, progression free interval; Sx, surgery; TSS, tumour specific survival.

gastrointestinal adverse events occurred in dogs that were treated with a combination of capecitabine and piroxicam ($n = 3$ grade 1, and $n = 1$ grade 2, respectively).

Overall, 8 (32.0%) dogs had their chemotherapy protocol discontinued for the following reasons: PD ($n = 4$) after a median of three cycles (range, 2–4), toxicity ($n = 2$) after two and four cycles, respectively, and lack of owner's compliance after 8 and 12 cycles ($n = 2$), respectively, with both dogs having SD.

5.3 | Outcome

Response to treatment was evaluable in the 22 (88.0%) dogs with macroscopic disease. There were 3 (13.6%) PR (1 colic adenocarcinoma, 1 colorectal carcinoma, both unresectable and metastatic to lymph nodes, and 1 hepatocellular carcinoma with nodal metastasis), 16 (72.7%) SD and 3 (13.6%) PD. The overall CB rate was 86.4%. Median duration of CB was 102 days (95% CI 55–154; range, 37–521; Figure 1).

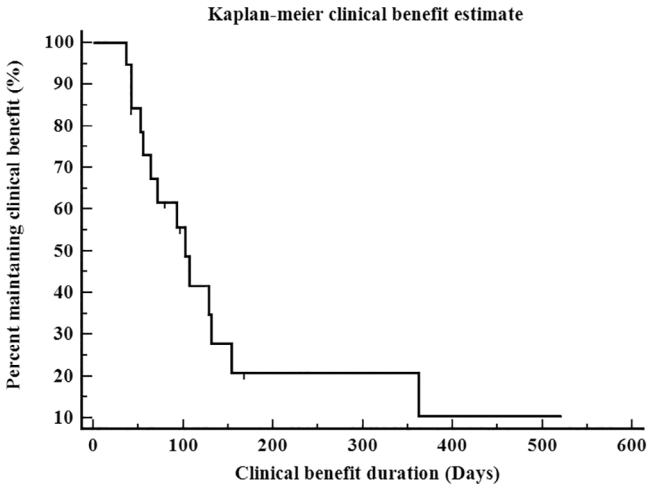

FIGURE 1 Kaplan–Meier curves showing CB duration in dogs with carcinoma receiving capecitabine (median CB, 107 days; 95% CI, 64–154 days). Censored: not progressed at the end of the study. CB, clinical benefit.

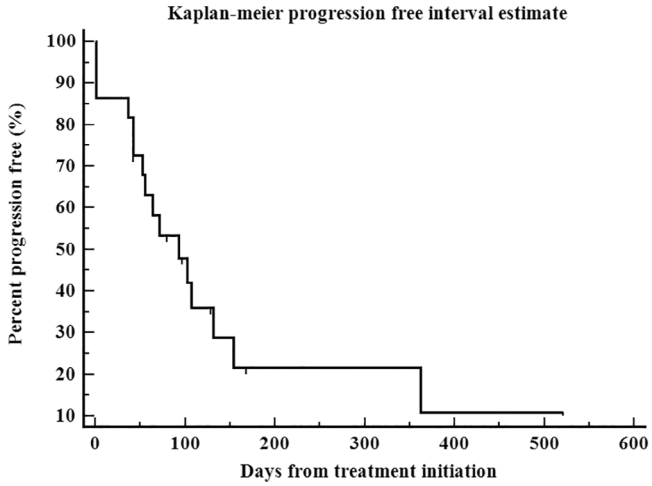

FIGURE 2 Kaplan–Meier estimations of PFI in dogs with carcinoma receiving capecitabine (median PFI, 107 days; 95% CI, 64–154 days). Censored: not progressed at the end of the study. PFI, progression-free interval.

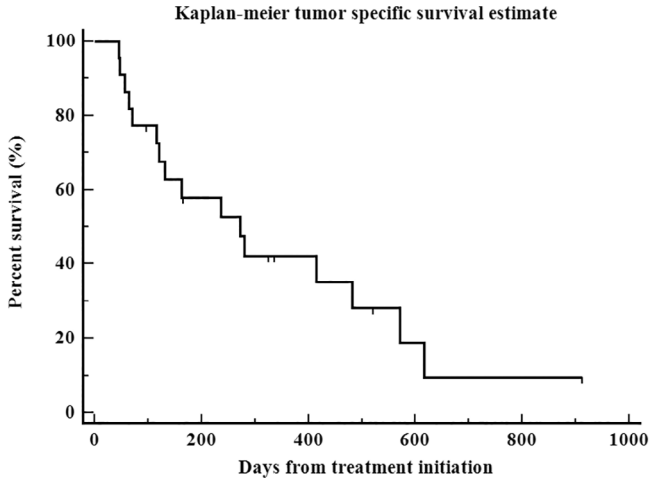

FIGURE 3 Kaplan–Meier estimations of overall TSS in dogs with carcinoma receiving capecitabine (median TSS, 405 days; 95% CI, 97–571 days). Censored: death by tumour-unrelated causes or alive at the end of the study. TTS, tumour-specific survival.

Median PFI was 93 days (95% CI 42–154; range, 1–521; Figure 2).

For the three dogs that received capecitabine in the microscopic setting, PFI was 118 days in one dog, while the others did not progressed after 352 and 405 days, respectively.

At data analysis closure, 21 (84.0%) dogs were dead, while 4 (16.0%) were still alive after a median follow-up of 337 days (range, 325–913) following capecitabine initiation and 426 days (range, 404–944) after primary cancer diagnosis. Among dead dogs, 17 (80.9%) died for cancer-related causes, while 4 (19.1%) for unrelated causes ($n = 1$, progression of chronic kidney disease, acute kidney injury, primary lung tumour, surgical wound dehiscence and sepsis).

Median TSS for the dogs with macroscopic disease was 273 days (95% CI 116–482; range 45–913; Figure 3). For the three dogs that received capecitabine in the microscopic setting, one dog with a thymic carcinoma was alive after 352 days, whereas the other two dogs were dead after 144 and 405 days, respectively.

Overall outcomes are reported in Table 1. None of the evaluated variables were significantly associated with CB, PFI or TSS (Table 2).

6 | DISCUSSION

Dogs with locally advanced and/or metastatic carcinoma of various origin have limited treatment options.[15–18] Capecitabine is a prodrug that offers the advantages of an orally-administered therapy with potentially fewer toxic effects than conventional bolus regimens. The management of cancer patients at home has been crucial during the pandemic. Indeed, the spread of COVID-19 has prompted many veterinary oncologists to develop different strategies for cancer.[22] Dogs that were undergoing intravenous chemotherapy or were ready to initiate chemotherapy after surgery were forced to suspend their treatment because of the pandemic. In the current series, 21 dogs (data not shown) were treated during the COVID-19 breakout, providing the unexplored opportunity to collect preliminary information regarding safety and antitumoral activity of capecitabine, a quite new cytotoxic drug to veterinary medicine, in dogs with biologically aggressive carcinoma.

TABLE 2 Influence of potential prognostic variables on CB, PFI and TSS of the 22 dogs with macroscopic carcinoma receiving capecitabine.

Variable		Median CB (days) (95% CI)	Events (n =)	p	Median PFI (days) (95% CI)	Events (n =)	p	Median TSS (days) (95% CI)	Events (n =)	p
Metastasis	Yes[15]	93 (42–131)	11/15	.19	71(37–107)	(13/15)	.14	163 (64–571)	(12/15)	.21
	No[7]	362 (55–362)	3/7		362 (1–362)	(3/7)		482 (56–617)	(4/7)	
Previous chemotherapy	Yes[8]	107 (53–154)	6/8	.72	102 (1–154)	(7/8)	.57	163 (70–617)	(8/8)	.87
	No[14]	93 (42–362)	8/14		71 (42–362)	(9/14)		236 (47–571)	(8/14)	
Previous Surgery	Yes[13]	107 (42–362)	9/13	.34	102 (37–154)	(11/13)	.83	163 (47–415)	(10/13)	.55
	No[9]	93 (42–129)	5/9		93 (1–93)	(5/9)		236 (56–617)	(6/9)	
Piroxicam administration	Yes[9]	93 (42–362)	4/9	.52	71 (1–362)	(7/9)	.61	121 (45–571)	(7/9)	.58
	No[13]	102 (55–154)	10/13		102 (53–154)	(9/13)		273 (56–617)	(9/13)	

Abbreviations: CB, clinical benefit; PFI, progression free interval; TSS tumour specific survival.

The safety profile in our preliminary analysis is very intriguing, with only 1 grade 3 toxicity episode overall. Adverse reactions occurred frequently (68.0%); however, none of the dogs developed long-term, irreversible toxicity; also, treatment discontinuation due to adverse events occurred in 2 (8.0%) dogs only, experiencing, respectively, grade 1 and grade 2 neurologic toxicity.

The most reported adverse events were gastrointestinal in nature, of low grade and self-limiting (12/17, 70.5%). It must be acknowledged that, among these dogs, 4 also received piroxicam, making it difficult to determine whether the adverse gastrointestinal signs were related to capecitabine, piroxicam, or both.

The frequency and severity of neurologic and ocular adverse events were lower in our population than in those previously reported.[11–13] In the current series, 5 dogs (5/17, 29.4%) experienced mild and short-lived neurologic and ocular toxicity, whereas in previous studies, in which capecitabine was used as part of an immunosuppressive protocol for renal transplantation, severe and unpredictable neurotoxicity and variable ocular toxicity occurred, resulting in four treatment-related deaths.[11,12] It is possible that the previously observed toxicity may have been due to the administration of immunosuppressive drugs, rather than to capecitabine.

Efficacy data analysis showed that 13.6% of the capecitabine-treated dogs achieved PR and 86.4% obtained CB, with a median PFI of 107 days and a median TSS of 273 days since the initiation of capecitabine. None of the evaluated variables was significantly associated with outcome. While these findings suggest that capecitabine is moderately active in treating dogs with biologically aggressive carcinoma, it is important to emphasize that the study encompassed dogs with vastly different tumour types, biological behaviours, tumour burden, stages, and staging modalities, in addition to a relatively small sample size.

There are several reasons that may explain the limited response rate. First, the greatest majority (72%) of dogs of our series had previously gone through the most active standard therapies before being submitted to the second line. Among them, 36% had already received chemotherapy, possibly contributing to the development of chemoresistance. Also, >50% had metastatic disease when treated with capecitabine, obviously negatively impacting prognosis. Finally, it may be possible that capecitabine dose or schedule was suboptimal, as the best treatment regimen has not been yet established.

In this series, 14 different histologic types of carcinomas were treated. Although the number of dogs within each tumour type was small, objective responses were documented for hepatocellular and colorectal carcinoma. Identification of a new chemotherapeutic agent potentially efficacious against these tumours in the macroscopic setting would be of great benefit, more over because standard-of-care treatment has not been identified.

These findings prompted us to review the human literature, finding some similarities. Indeed, in humans with colorectal cancer, capecitabine is the only oral fluoropyrimidine that has shown efficacy equivalent to 5-fluorouracil, leading to its regulatory approval worldwide for this indication.[23]

In veterinary medicine, data relating to the medical treatment and outcome of dogs with colic and colorectal adenocarcinoma are limited. A retrospective study reported a mean survival time of 1.6 months for dogs with luminal/annular adenocarcinoma that did not undergo surgical or medical treatment.[24]

In our population, 2 of the 3 PR concerned dogs with inoperable colic and colorectal adenocarcinoma with node metastasis. For both dogs, PFI was approximately 90 days; one died because of intraoperative complications following removal attempt of the colon carcinoma, whereas the other died 571 days after the starting of capecitabine. Additional studies are necessary to better understand the therapeutic efficacy of capecitabine in this clinical context.

Capecitabine is also considered a potentially effective drug against human advanced HCC,[25] both as first-line and post-sorafenib treatment, and may even represent a cure for a certain subgroup of patients.[26]

In dogs, nodular HCC carries a poor prognosis, while massive HCC is typically slow growing and associated with a more favourable prognosis following surgical excision.[27] In the current series, three dogs had nodular HCC and three had massive HCC. One dog with massive HCC underwent liver lobectomy, and was diagnosed with nodal metastatic disease when capecitabine was started, obtaining PR. The remaining five dogs with measurable disease experienced SD. At data analysis closure, three of six dogs were alive after a median follow-up of 267 days (range, 78–627), whereas three had died with a median TSS of 271 days (range, 56–521).

The main limitations of our study arise from the small population analysed and its retrospective nature. This series was heterogeneous in relation to cancer type, stage, tumour burden at the initiation of capecitabine (microscopic vs. macroscopic disease) and type of preceding therapy lines. Staging procedures and intervals were not standardized. Moreover, the lack of a control group does not allow to compare outcome results. Last, it is worth mentioning that 36% of dogs were also receiving piroxicam; therefore, we cannot exclude the possible contribution of this drug to the response rate, even though for none of them a response to single agent piroxicam was reported.

In conclusion, considering the overall toxicity profile, capecitabine seems advantageous not only because it selectively accumulates in tumour cells by nature of its mechanism of action, thereby sparing normal cells, but also because dogs with advanced carcinoma are not cured with current treatments, and palliation is the most important goal of therapy. Additional studies are necessary to optimize the scheduling of capecitabine and to determine its efficacy for selected epithelial tumours in dogs in both, the macroscopic and microscopic setting.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Agnoli C, Rimondi S, Ghisoni G, et al. Spotlight on capecitabine for the treatment of unresectable or metastatic carcinoma of various origin: A retrospective study of 25 dogs. *Vet Comp Oncol*. 2023;1-7. doi:10.1111/vco.12945