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A Randomized Trial Investigating the Efficacy and Safety of Water Soluble Micellar Paclitaxel (Paccal Vet) for Treatment of Nonresectable Grade 2 or 3 Mast Cell Tumors in Dogs

D.M. Vail, **H. von Euler**, **A.W. Rusk**, **L. Barber**, **C. Clifford**, **R. Elmslie**, **L. Fulton**, **J. Hirschberger**, **M. Klein**, **C. London**, **M. Martano**, **E.A. McNiel**, **J.S. Morris**, **N. Northrup**, **B. Phillips**, **G. Polton**, **G. Post**, **M. Rosenberg**, **D. Ruslander**, **A. Sahora**, **S. Siegel**, **D. Thamm**, **S. Westberg**, **J. Winter**, and **C. Khanna**
Department of Medical Sciences, School of Veterinary Medicine and the Carbone Comprehensive Cancer Center, University of Wisconsin—Madison, Madison, WI (Vail); The Department of Veterinary Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden (von Euler); Animal Clinical Investigation, Washington, DC (Rusk); Department of Clinical Services, Oncology, Tufts Cummings School of Veterinary Medicine, North Grafton, MA (Barber); Red Bank Veterinary Hospital, Tinton Falls, NJ (Clifford); Veterinary Cancer Specialists, Englewood, CO (Elmslie); MedVet, Worthington, OH (Fulton); Ludwig-Maximilian University, Munich, Germany (Hirschberger); Southwest Veterinary Oncology, Tucson, AZ (Klein); Department of Veterinary Biosciences, The Ohio State University, Columbus, OH (London); Department of Animal Pathology, Faculty of Veterinary Medicine, Italy (Martano); Michigan State University, Department of Small Animal Clinical Sciences, East Lansing, MI (McNiel); School of Veterinary Medicine, University of Glasgow, UK (Morris); Department of Small Animal Medicine, University of Georgia College of Veterinary Medicine, Athens, GA (Northrup); Veterinary Specialty Hospital of San Diego, San Diego, CA (Phillips); North Downs Specialist Referrals, Bletchingley, Surrey, UK (Polton); Veterinary Oncology and Hematology Center, Norwalk, CT (Post); Veterinary Cancer Group of Orange County, Tustin, CA (Rosenberg); Veterinary Specialty Hospital of the Carolinas, Cary, NC (Ruslander); The Oncology Service, LLC, Friendship Hospital for Animals, Washington, DC (Sahora); New England Veterinary Oncology Group, Waltham, MA (Siegel); Colorado State University College of Veterinary Medicine, Animal Cancer Center, Fort Collins, CO (Thamm); Faculty of Veterinary Medicine and Animal Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden (Westberg); Southeast Vet Oncology, Orange Park, FL (Winter); and The Oncology Service, LLC, Friendship Hospital for Animals, Washington, DC (Khanna).

Abstract

Background—Effective treatments for dogs with advanced stage mast cell tumors (MCT) remain a pressing need. A micellar formulation of paclitaxel (paclitaxel [micellar]) has shown promise in early-phase studies.

Hypothesis/Objectives—The objective was to demonstrate greater activity for paclitaxel (micellar) compared with lomustine. The null hypothesis was $\mu_p = \mu_L$ (ie, proportion of responders for the paclitaxel [micellar] and lomustine groups, respectively).

Corresponding author: D.M. Vail, DVM, DACVIM, Department of Medical Sciences, School of Veterinary Medicine and the Carbone Comprehensive Cancer Center, University of Wisconsin—Madison, 2015 Linden Drive, Madison, WI 53706; vaild@svm.vetmed.wisc.edu..

Animals—Two hundred and fifty-two dogs with advanced stage nonresectable grade 2 or 3 MCT.

Methods—Prospective multicenter randomized double-blind positive-controlled clinical trial. The primary endpoint was confirmed overall response rate (CORR) at 14 weeks. A secondary endpoint, biologic observed response rate (BORR), also was calculated. Safety was assessed by the characterization and grading of adverse events (AE).

Results—Overall CORR (7% versus 1%; $P = .048$) and BORR (23% versus 10%; $P = .012$) were greater for paclitaxel (micellar) compared with lomustine. Paclitaxel (micellar)-treated dogs were 6.5 times more likely to have a confirmed response and 3.1 times more likely to experience a biologic observed response. The majority of AE with paclitaxel (micellar) were transient and clinically manageable. Twenty-seven dogs (33%) receiving lomustine were discontinued because of hepatopathy compared with 3 dogs (2%) receiving paclitaxel (micellar) ($P < .0001$; odds ratio 26.7).

Conclusions and Clinical Importance—Paclitaxel (micellar)'s activity and safety profile are superior to lomustine. The addition of an active and novel taxane to the veterinary armamentarium could fill a substantial need and, as its mechanism of action and AE profile do not overlap with currently available TKI, its availability could lead to effective combination protocols.

Keywords

Cancer; Canine; Chemotherapy; Paclitaxel; Taxane

MCT is the most common cutaneous tumor in the dog, accounting for nearly one-fifth of all skin tumors encountered in companion (pet) dogs.[1] Surgical excision or surgical cytoreduction followed by radiation therapy is the treatment of choice for early stage, low, and intermediate grade MCT in dogs. However, of pressing clinical need in the current practice of veterinary oncology are effective and safe treatment options for companion dogs with macroscopic (gross) advanced stage disease not amenable to surgical excision, in regions lacking available radiation facilities, or when high-grade MCT increases the likelihood of recurrence and distant metastasis after surgery. With few exceptions, advanced stage, nonsurgical MCT is a uniformly progressive and fatal disease in dogs.

At present, no cytotoxic-class chemotherapeutics exist that are registered for treatment of solid tumors in dogs. Two small molecule tyrosine kinase inhibitors (TKI) (toceranib and masitinib) are registered for use in macroscopic MCT in dogs. Their mechanism of action primarily targets the c-kit TK growth factor receptor, a receptor that is known to be mutated and aberrantly expressed in approximately 25–30% of grade II/III MCT encountered in companion dogs.[2–5] This leaves a continued need for cytotoxic chemotherapeutics that are active against MCT in dogs and the primary mechanism of action of which is not dependent on the presence or inhibition of c-kit.

The current practice of veterinary oncology relies, for the most part, on the extra-label use of chemotherapeutics registered for use in humans. The 2 most commonly used cytotoxic agents currently thought to have activity against canine MCT disease are lomustine and vinblastine.[1,6–12] These agents have not been subject to rigorous GCP-standard field trials[13] and their safety and activity in companion dogs therefore is considered to be anecdotal.

Taxane-class chemotherapeutics (eg, paclitaxel) are the most widely prescribed cytotoxic therapies in human oncology based on their broad-spectrum activity across several tumor histologies and their predictable safety profile.[14] Taxol (Bristol-Myers Squibb, Princeton, NJ), the most widely used formulation of paclitaxel, requires Cremophor EL as an excipient to allow water solubility for parenteral delivery. Taxol has shown activity in dogs with

malignant tumors; however, adverse events are common with this formulation and the majority of dogs experience allergic or anaphylactic hypersensitivity reactions to the cremophor excipient despite receiving premedication with antihistamines and corticosteroids.[15] A new formulation of paclitaxel (Paccal Vet[a]) that is made water-soluble by using a mixed micellar preparation with a surfactant based on derivatives of retinoic acid (referred to as paclitaxel [micellar] from here forward) has recently been developed.[16] The excipient in paclitaxel (micellar), retinoid-derived XR-17, has not resulted in systemic toxicity in normal laboratory dogs (unpublished data). Furthermore, 32 dogs that received paclitaxel (micellar) in an open-label clinical study experienced dose-limiting neutropenia at day 4 at 175 mg/m^2 whereas a mean dose of 150 mg/m^2 generally was well tolerated.[16] Other adverse events reported in these dogs include alopecia, transient inappetence and vomiting, diarrhea, or both.

The objective of the field trial reported here was to document the safety and efficacy of paclitaxel (micellar) in companion dogs with macroscopic advanced nonresectable MCT in the context of a GCP-compliant, randomized, controlled clinical trial (versus lomustine).

Materials and Methods

Trial Design

The study was designed as a randomized double-blind positive-controlled confirmatory clinical field study and was conducted by veterinary oncologists at sites in the United States (n = 17) and the European Union (n = 5) in compliance with good clinical practice (GCP).[17] The protocol was deemed acceptable by the US Food and Drug Administration Center for Veterinary Medicine and was reviewed and approved by European Union regulatory and ethics committees. Owner informed consent was obtained in writing before initiating study-related procedures.

Dog Selection and Discontinuation

Client-owned dogs presented between October 2008 and March 2010 with nonresectable grade 2 or 3 MCT (clinical stage 2a or 3a) that were of any age, sex, or breed and weighed at least 5 kg were screened for enrollment. Dogs were excluded from enrollment for any of the following reasons: (i) pregnant, lactating, or intended for breeding; (ii) life expectancy <1 month, (iii) performance status score[18] of ≥ 3; (iv) absolute neutrophil count $<2.0 \times 10^9$/L, platelet count $<100 \times 10^9$/L, bile acid concentrations, alanine aminotransferase (ALT) activity, or alkaline phosphatase (ALP) activity > twice the upper limit of normal (ULN), serum creatinine concentrations > ULN; (v) previous or concurrent treatment with any chemotherapeutic agent, target lesion radiation, hormonal, immunological (including antiandrogens), or biologic treatment; (vi) systemic corticosteroid treatment within 3 weeks of the study; (vii) active infection or any concurrent disease that would require additional therapy and could result in death of the dog within 3 months; or (viii) enrollment in another clinical trial.

Study dogs were removed from the study if any of the following occurred: (i) clinically relevant hepatopathy (ALT > twice ULN or more than twice the activity observed at baseline); (ii) progressive disease (PD); (iii) clinically relevant adverse events, treatment delay > 31 days from previous cycle or both; (iv) or withdrawal of owner consent or protocol noncompliance.

[a]Paccal Vet solution for infusion, 1 mg/mL; Oasmia Pharmaceutical AB, Uppsala, Sweden

Study Treatments

Study dogs were randomly allocated (see Statistical Analysis) to treatment with a 2 : 1 ratio to receive paclitaxel (micellar)[a] (150 mg/m^2 IV) or lomustine[b] (70 mg/m^2 PO), respectively. An unblinded treatment administrator administered treatments on Day 0 of each of 4 consecutive 21-day cycles (Table 1). Paclitaxel (micellar) was supplied as 60 mg of lyophilized powder in 100- or 75-mL vials, which were reconstituted in 60 mL of Ringer's acetate to a paclitaxel (micellar) concentration of 1 mg/mL. The reconstituted paclitaxel (micellar) was immediately infused IV slowly over 15 to 30 minutes. Lomustine was provided as capsules for PO administration (10 and 40 mg capsules; for individual dogs, rounding up or down to the nearest 10 mg was allowed).

The dosage of paclitaxel (micellar) had been established from previous studies.[16,19] Lomustine was chosen as the positive control because other appropriate veterinary-registered treatments were not available when the study was initiated, anecdotal activity of lomustine in canine MCT was documented in the veterinary literature,[10,11] and its 3-week treatment cycle was consistent with 3-week intervals used with paclitaxel (micellar). The rationale for and dose of lomustine were adopted from the literature and consultation with key opinion leaders in veterinary oncology.[1,10,11]

Randomization, calculation of study drug dosages, and administration of study drugs were performed by an unblinded treatment administrator. The treatment administrator was prohibited from making efficacy assessments. As the route of administration differed between treatment groups, a forelimb of every dog was shaved and bandaged by the treatment administrator, regardless of treatment to blind those assessing efficacy.

Dose reductions or delays were permitted by the protocol because of dose-limiting toxicity (DLT) defined as grade III or IV toxicity according to the Veterinary Comparative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE v1.0).[20] The maximal allowable duration of delay was 31 days, after which the animal was withdrawn from the study. Dose reductions for paclitaxel (micellar) were permitted in decrements of 10 mg/m^2, and lomustine by at least 10 mg per dog.

No concomitant anticancer therapies (chemotherapy, immunotherapy, hormonal cancer treatment, systemic corticosteroids, radiation treatment, experimental cancer therapies or NSAID) were permitted during the study. In the presence of severe neutropenia or fever, antibiotics were administered at the discretion of the investigator. Maropitant (2 mg/kg PO or 1 mg/kg SQ) was recommended as an antiemetic if emesis was observed, but was not used prophylactically.

Clinical Assessments

Treatment and assessment events are summarized in Tables 1 and 2. An investigator blinded to treatment always made efficacy assessments, and data collected from unblinded and blinded personnel were recorded in 2 separate study binders. After obtaining written owner consent, the investigator performed a screening examination within 14 days before the start of the first treatment cycle. Screening examinations included a medical history and physical examination (including body temperature and weight). Concurrent disease or conditions that might influence tumor progression or treatment were noted, and demographic information was recorded. Concomitant medications were recorded at all visits. Physical examinations were performed, and performance status assessed[18] at all visits. The owner was asked to

[b]CeeNU, 10, 40, and 100 mg oral capsules; Bristol-Myers Squibb, Princeton, NJ

specifically record episodes of perceived nausea, vomiting, and diarrhea in the intervals between all visits.

Each dog's MCT was evaluated during the study, per RECIST (v1.0)[21] which required at least 1 measurable lesion. Target lesions were selected on the basis of their size (lesions with the longest diameter) and their suitability for repeatable measuring. A sum of the longest diameter for all target lesions was calculated and reported as the baseline sum of the longest diameter. Biopsy and histopathology were required to confirm the diagnosis of all target lesions (within 6 months before or at the screening visit) and tumors were graded according to Patnaik.[22] Lymph node presence or absence of mast cells was confirmed by fine needle aspiration and cytology. All measurable primary lesions (up to a maximum of 5) representative of the skin and if applicable a maximum of 5 regional lymph node lesions were to be identified and measured as target lesions (a maximum of 10 total target lesions). Calipers were used to measure target lesions and a digital camera was used to document the measurements. The measurements were performed by the blinded investigator throughout the study. All other lesions (or sites of disease) were classified as nontarget lesions. Measurements of all nontarget lesions were not required, but presence or absence of each was noted at Visits 13 and 14. Tumor staging was performed according to the WHO classification system[23] by abdominal ultrasound examination, lymph node palpation, and fine needle aspiration of enlarged lymph nodes. Thoracic radio-graphs were recommended, but not required, if the target lesion was located cranial to the insertion of the diaphragm. Tumor staging was repeated at Visits 13 and 14.

Blood and urine samples were collected at most visits (Table 2) for routine hematology (CBC), serum biochemistry (including alanine aminotransferase [ALT], alkaline phosphatase [ALP] and aspartate aminotransferase [AST] activities), and urinanalyses.

Efficacy Assessments

The study's primary *a priori* regulatory endpoint was confirmed overall response rate (CORR) from tumor assessments according to RECIST (v1.0).[21] Response outcome was categorized as complete response (CR; disappearance of all target lesions); partial response (PR; ≥ 30% decrease in the sum of the longest diameters [LD] compared with baseline); progressive disease (PD; ≥ 20% increase in the sum of the LD compared with the smallest measured sum at any visit); and stable disease (SD; any change not qualifying as CR, PR or PD). CORR (yes or no) for each study dog was defined as complete response (CR) or partial response (PR) of target and nontarget lesions and no new lesions at Visit 13, and the overall response were confirmed at Visit 14 (only responses confirmed at Visit 14 were eligible to be counted). Dogs were considered as responders at Visit 14 if they satisfied at least 1 of the following 3 treatment outcomes: (i) target and nontarget lesions observed with CR, and no new lesions; (ii) target lesions observed with CR, and nontarget lesions observed with PR or SD, and no new lesions; (iii) target lesions observed with PR, and nontarget lesions observed with non-progressive disease, and no new lesions. All other dogs were considered nonresponders.

A secondary efficacy endpoint, biologic observed response rate (BORR), often referred to as *Clinical Benefit*, which combines the stable disease (SD) rate with the CR and PR rate, also was assessed at Visit 13 and confirmed at Visit 14.

Exploratory Comparison of Activity—At the completion of study, more conventional assessments of clinical activity were assessed including best overall response rate (BESTORR), defined as PR or CR across all measurement time points[24] and progression-free survival (PFS) rate at 6 weeks were calculated post hoc in dogs receiving either treatment to allow comparison of activity with those of TKI and unregistered (off-label)

cytotoxic agents used in dogs with MCT and reported in the veterinary literature using these end-points.

Safety Assessments

Abnormal clinical examination findings, clinically relevant laboratory abnormalities, or other clinically relevant observations were reported as adverse events. Adverse events (AE) were recorded spontaneously at any time point during the study and were defined as any undesirable event, expected or not, occurring in a dog during the study, whether considered as having a causal relation to study treatment or not. Adverse events were classified according to the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) and graded according to VCOG-CTCAE (v1.0).[20,25]

Statistical Analysis

Randomization was conducted with a 2:1 treatment allocation with a web-based centralized randomization program.[c] Tumor grade (grade 2 or 3) and stage (stage 2 or 3) were used as stratification factors. The number of dogs in each stratum was not predetermined and was dependent upon actual accrual. In particular, there was no requirement for the strata to have equal sizes. According to the protocol, 243 dogs were to be randomized to the study. The study was originally powered (80%) to detect a 20 percentage unit difference between treatments assuming an initial lomustine response rate of 50% (target of 225 dogs, with 252 dogs actually randomized). However, because of the unexpectedly low response rate, enrollment numbers were subsequently increased relative to the original power estimate. A treatment administrator handled the centralized computer randomization system at each study site. Each randomized dog was allocated a sequential randomization number by the central randomization system. The randomization system produced an electronic copy stating the date and time of randomization and the dog's randomized study treatment.

The objective of this study was to demonstrate a statistically greater CORR after 4 treatment cycles according to RECIST v1.0 for paclitaxel (micellar) compared with lomustine. The null hypothesis was $\mu_p = \mu_L$ (ie, the proportion of confirmed overall responders for the paclitaxel [micellar] and lomustine groups, respectively). CORR was analyzed with exact logistic regression that included the main effect of treatment group and the stratification variables: tumor grade and tumor stage. Attributable to an unexpectedly low responder rate in this study, the interaction between treatment and stratification variables could not be included in the statistical models. The 95% confidence intervals and odds ratios were calculated. These same analyses also were used for the secondary endpoint of BORR assessments.

Group comparisons for other variables were considered exploratory; nonetheless treatment groups were compared with Fischer exact or Chi-square tests for categorical variables, Cochran-Mantel-Haenszel tests controlling for the stratification factors (tumor grade and tumor stage) for ordinal variables, and Mann Whitney *U*-tests for continuous variables. Wilcoxon matched-pair signed rank test was used for changes from baseline for each treatment group, separately, for continuous variables. Kaplan–Meier methodology was used to investigate treatment differences in discontinuation rate. All statistical tests were conducted with SAS,[d] and were 2-sided with a significance level of 5%.

[c]International Drug Development Institute, Louvain-la-Neuve, Belgium
[d]SAS v9.1.3; SAS Institute Inc, Cary, NC

Results

Demographic Information

Of the 252 randomized dogs (Table 3), 249 dogs with a mean ± SD age of 8.7 ± 2.8 years (range, 1 month–14.6 years) and weight of 28 ± 13 (range, 5–70) kg received at least 1 dose of study treatment. Female dogs (56%) outnumbered male dogs (44%) and most dogs (89%) were neutered. Dogs from 49 breeds were represented: the most common breeds were mixed breed (24%), Labrador Retriever (19%), Boxer (10%), Golden Retriever (9%), and Pug (4%). Dogs with grade 2 tumors (68%) were more prevalent in the study compared with those with grade 3 tumors (32%), and most dogs (86%) had advanced stage (stage 3a) tumors. Mean age and weight and distribution of sex, neuter status, breed, and tumor grade or stage were not different between treatment groups (Table 4).

One paclitaxel (micellar) dog with a stage 1a tumor was inadvertently enrolled in the study. Megestrol acetate, a prohibited concomitant treatment, was inadvertently administered to 19 dogs by 1 investigator as part of that clinic's normal protocol for appetite simulation for cases with persistent or severe anorexia. These 20 dogs were excluded from a per-protocol (PP, n = 229) analysis of efficacy. The results regarding the primary efficacy analysis obtained from the PP compared with the intention to treat (ITT, n = 252) populations were numerically and directionally similar, but the PP analysis lacked statistical power to demonstrate a statistically significant result. Nonetheless, according to the *a priori* statistical analysis plan and published statistical regulatory guidance for conducting superiority clinical trials,[26] the ITT population was finally used for making inference on efficacy and safety.

More paclitaxel (micellar) dogs received all 4 cycles of treatment and completed the study compared with lomustine dogs (Table 3 and Fig 1). The most common reason for discontinuation of paclitaxel (micellar) was progressive disease, whereas lomustine was most commonly discontinued because of hepatopathy or progressive disease. The death rate, including euthanasia (9%), was similar between treatments.

Clinical Efficacy

Overall CORR, the *a priori* primary endpoint, was significantly greater (7 versus 1%; $P = .048$) for paclitaxel (micellar) compared with lomustine (Table 5). Paclitaxel (micellar)-treated dogs were 6.5 times more likely, compared with lomustine-treated dogs, to have a confirmed response (CR or PR) at 14 weeks (Visit 14, 35 days after 4 cycles of treatment). When dogs with a response of SD were included in supplemenary analysis, BORR (*Clinical Benefit*) was significantly greater (23 versus 10%; $P = .012$) for paclitaxel (micellar) compared with lomustine (Table 5). Paclitaxel (micellar)-treated dogs were 3.1 times more likely, compared with lomustine-treated dogs, to have a confirmed BORR (CR, PR, or SD) at 14 weeks.

Exploratory Comparison of Activity—The BESTORR and the 6-week PFS rate for paclitaxel (micellar), calculated post hoc, was 23 and 68%, respectively, and for lomustine was 23 and 66%, respectively.

Clinical Safety

Clinically relevant AE in both treatment groups, with respect to laboratory results and physical examination or vital sign abnormalities, were observed in 167 (of 168) paclitaxel (micellar) dogs and 80 (of 81) lomustine dogs (summarized in Table 6). Most non-hematologic AE were graded as nonsevere (grade <3). Hematologic (in particular neutropenia) and gastrointestinal (emesis, anorexia, and diarrhea) events were the most

common reported AE in paclitaxel (micellar)-treated dogs. Hematologic and hepatic events were the most common reported AE in lomustine-treated dogs.

Relative to baseline results, neutrophil count was consistently lowest on Day 4 of each cycle for both treatment groups, and had generally returned to baseline by Day 0 of the following cycle (Fig 2). Most neutropenia events in paclitaxel (micellar)-treated dogs were because of grade 3 and 4, transient, clinically silent neutropenia; only 6 cases (4%) were accompanied by grade 3 or 4 pyrexia and only 2 (1%) resulted in treatment discontinuation.

Increases in hepatic enzyme activity (ALT, AST, ALP), relative to baseline, were greater for lomustine compared with paclitaxel (micellar) dogs. Twenty-seven dogs (33%) in the lomustine group were discontinued because of hepatopathy compared with 3 (2%) in the paclitaxel (micellar) group ($P < .0001$; odds ratio 26.7). The majority of lomustine dogs that developed clinically relevant hepatopathy (as measured by grade 3 increases in ALT activity) leading to discontinuation did so at Visit 8 (just before the 3rd cycle of treatment).

The incidence of perceived nausea, vomiting, and diarrhea generally was highest on Day 4 of each cycle (Table 7). More paclitaxel (micellar) dogs were observed with these 3 events on Day 4 of each cycle, compared with lomustine dogs. The incidence of these events (on Day 4 of each cycle) decreased with time.

The incidence of physical examination abnormalities was relatively low during the study. Mean body weight (approximately 28 kg), body temperature (approximately 39°C), and mean change in body temperature from baseline were similar between treatment groups and over time. Mean change in body weight, relative to baseline, decreased over time for both groups and was greatest (− 1.3 kg) for paclitaxel (micellar) dogs on Visit 9 (Day 4 of Cycle 3). The percentage of paclitaxel (micellar) dogs with a performance status score of ‘normal’ was lowest on Day 4 after treatment and highest by Day 0 of the following treatment cycle (Table 7). The percentage for normal paclitaxel (micellar) dogs tended to be numerically lower than for lomustine dogs throughout the study.

Approximately 42% of dogs in both treatment groups required a dose reduction at 1 or more cycles during the study; slightly fewer paclitaxel (micellar) dogs (9%) required a dose delay compared with lomustine (14%). The mean dose of paclitaxel (micellar) per dog was numerically lower for Cycles 2 through 4 (130 ± 43 mg) compared with Cycle 1 (134 ± 46 mg), with an average dose change of −12% in dogs over 4 cycles of treatment. The mean dose of lomustine per dog decreased with cycle from 62 ± 21 to 53 ± 19 mg. The average dose change over time was similar between paclitaxel (micellar) (−12%) and lomustine (−10%).

The most commonly (31–76% of dogs) administered concomitant medications were (in descending order) diphenhydramine, famotidine, maropitant, electrolytes, metronidazole, amoxicillin, enrofloxacin, and metoclopramide. Other therapies concurrently administered during the study were megestrol, tramadol, ampicillin, sucralfate, butorphanol, cephalexin, ondansetron, ciprofloxacin, sulfa drugs, loperamide, omeprazole, atipamezole, ivermectin, dexmedetomidine, marbofloxacin, glucosamine, methionine, mirtazapine, fipronil, multivitamins, filgrastim, and levothyroxine.

Discussion

Paclitaxel (micellar) is active against macroscopic advanced nonresectable MCT in dogs and has a safety margin consistent with cytotoxic chemotherapeutic class agents. Both activity and safety were superior to lomustine. Addition of an active and novel taxane to the veterinary armamentarium could fill a substantial need in the field. Its mechanism of action

and dose-limiting AE profile do not substantially overlap with currently available TKI, and as such its availability could lead to effective combination protocols, which are the current treatment paradigm in medical oncology.

The 7% CORR at 14 weeks for dogs receiving paclitaxel (micellar), although numerically modest, was nevertheless statistically significant ($P = 0.048$) compared with the positive comparator (lomustine), a drug described in the literature and understood by veterinarians to be active in MCT. Although CORR is a reasonable choice for a regulatory endpoint for a cancer drug, it is not a sufficient measure of clinical benefit and does not adequately portray the therapeutic benefit of an agent in the context in which it is to be used. Direct clinical benefit also should be interrogated as it relates to (i) the BORR, as the inclusion of stabilization of disease, along with the CR and PR rate, over a 14-week period can reasonably be assumed to translate into clinical benefit; (ii) comparable documented efficacy observed with therapeutic agents that have been granted regulatory authorization for this indication; (iii) comparable documented efficacy and expectations observed with unregistered cytotoxic agents currently used off-label by the veterinary oncology community for this indication.

When one considers BORR, the rate of 23% for paclitaxel (micellar)-treated dogs and 10% for lomustine dogs at the 14-week confirmation point ($P = .012$) again confirms superior clinical benefit over the “active” lomustine comparator. The rationale for inclusion of SD along with CR/PR, now routinely considered in response evaluations[20] is that nonprogression of tumors over 14 weeks translates into clinical benefit in a disease that if progressive, results in morbidity and ultimate mortality in the patient. Therefore, approximately one-quarter of companion dogs with advanced, macroscopic MCT disease experienced *Clinical Benefit* from paclitaxel (micellar) for at least 14 weeks.

When comparing efficacy observed with currently registered therapeutic agents, 2 TKI agents currently are approved for use in dogs with MCT (toceranib and masitinib). Paclitaxel (micellar) has a spectrum advantage over TKI in that its mechanism of action is independent of aberrant c-kit function (present in only 25–30% of gradeII/III MCT where TKI treatment has its greatest benefit)[2,3] and, therefore, paclitaxel (micellar) with measurable efficacy regardless of c-kit status would fill an important need. Regarding toceranib, the published BORR at 6 weeks was documented to be 60%[2] which also translates into the 6-week progression-free rate. The 6-week BORR for paclitaxel (micellar), calculated from raw data in the current trial, compares favorably at 68%. Furthermore, although a placebo (no treatment) group was not included in the current trial, the 68% 6-week PFS rate (32% progression) is substantially better than the placebo (no treatment) groups in 2 previous GCP-compliant registration trials for advanced mast cell disease.[2,3] In these previous studies, over 50% of dogs experienced PD within 3 weeks and over 70% within 6 weeks of placebo treatment, a circumstance that can reasonably be associated with the ultimate death of the patient.

In addition, when comparing efficacy with unregistered cytotoxic agents currently used off-label by the veterinary oncology community, paclitaxel (micellar) was superior to the positive lomustine control used in this trial. Moreover, the only 2 published studies assessing single-agent conventional-dose weekly vinblastine (2.0 mg/m^2) without prednisone reported BESTORR of 12%.[10,27] The BESTORR of 23% for paclitaxel (micellar) determined in the exploratory posthoc calculations used in a similarly advanced MCT bearing population (without prednisone) compares favorably. These interpolative and comparative data further demonstrate the clinical benefit of paclitaxel (micellar).

Unexpectedly, lomustine greatly underperformed in this field trial when considering anecdotal activity reports in the veterinary literature.[10] Several explanations exist, including (i) GCP assessments are more stringent compared with anecdotal (non-GCP) assessments and often document less robust activity; (ii) the high discontinuation rate because of hepatotoxicity and; (iii) the use of less stringent end-points in previously published non-GCP reports of lomustine use in dogs with MCT. This later point is particularly germane, in that most prior reports utilize best overall response rate (BESTORR), defined as the CR/PR rate at any time point during study, without the use of a final confirmatory time point, as was the case in this study. This allows response assessment to be performed before development of hepatotoxicity. Therefore, most prior studies reported activity by 6 weeks, whereas the 33% discontinuation rate (typically occurring before the 3rd treatment cycle) in the study reported here resulted in removal from trial before the 14-week confirmation of assessment visit. This serves to further illustrate the importance of GCP trial management and equality of end-point measures when evaluating and comparing agents.

Regarding the type and temporal nature of AE experienced and their likely impact on patient well-being, of the 85% grade 3 and 17% grade 4 incidence observed with paclitaxel (micellar), most were because of transient grade 3 and 4 neutropenia (73% grade 3 and 11% grade 4). With paclitaxel (micellar), chemotherapy-induced neutropenia (CIN) nadirs occurred early, were transient, and in most cases recovered in time to allow subsequent treatment cycles to occur (only 1% resulted in treatment discontinuation). CIN events in dogs generally were devoid of clinical signs and most dogs in the field trial remained afebrile (only 4% had serious or severe pyrexia). As such, although CIN is technically serious and life threatening, the majority of dogs maintained good quality of life.

When CIN is excluded from the AE incidence rate, the remainder of severe (12%) and serious (6%) AE primarily were confined to the gastrointestinal (GI) tract. Effects on the GI tract generally were transient and recovery occurred in sufficient time to allow treatment continuation. Unlike CIN, gastrointestinal adverse events (eg, perceived nausea, vomiting, anorexia, and diarrhea) have substantially more potential to affect quality of life. That severe and serious GI AE occur in the minority of cases provides less of a counterbalance to benefit and also must be considered in the context of our current ability to apply proactive and reactive treatment measures that would prevent or alleviate their impact on quality of life. This field trial, by its very nature, was designed only to react to AE as they developed rather than to be proactive by use of prophylactic antiemetic and antidiarrheal agents. Prophylactic care is the current standard of care in veterinary patients undergoing cytotoxic chemotherapy.[28] Therefore, the incidence of severe or serious AE with quality of life consequences is likely overstated. Importantly, many of the GI AE reported in this trial reflect those occurring during the natural history of advanced MCT. As such, the assessment of risk must first account for the baseline events that are associated with MCT progression. The nature of these events is tied to the systemic inflammatory biology of MCT and can affect many organ systems. Studies leading to registration of toceranib include an informative placebo population; during the initial 6-week study phase, AE occurred in 80% of the dogs that received placebo (16% severe).[2]

Overall, although the safety margin for paclitaxel (micellar) is low and the incidence of serious AE is high, the vast majority of AE are transient, manageable, and recovery occurs in time for subsequent cycles. Only 3 (2%) dogs died or were euthanized because of conditions likely to be related to these events. No unique AE were documented for paclitaxel (micellar) when compared with similar cytotoxic agents; therefore use will not require additional veterinary or client education or interventions, and the comfort level is similar to other agents currently employed. Furthermore, replacement of cremophor excipient with the

much safer excipient (XR-17) in paclitaxel (micellar) is a clear benefit to the currently available, off-label usage of other formulations of paclitaxel.

Limitations of the current trial include the use of *a priori* activity endpoints that did not include a temporal measure, such as PFS. That being said, the raw data were available to calculate a 6-week PFS rate and BESTORR that allowed exploratory comparisons with other registered and off-label agents currently used in veterinary oncology practice. In addition, the high discontinuation rate experienced in the lomustine-treatment group because of hepatotoxicity led to a substantial population unable to continue to the 14-week conformation assessment. However, this replicates practical use of lomustine where AE require consideration when continuing treatment. It is possible that if sufficient discontinuation time were allowed for liver enzyme activity to normalize in those patients, the resumption of lomustine treatment at decreased dose or prolonged intertreatment intervals would have resulted in some clinical benefit to the population, but this trial was not designed for that purpose. Furthermore, recent work by Skorupski and others has documented that denamarin partially abrogates hepatic AE in dogs receiving lomustine and the addition of this protectant may allow more consistent continuation of lomustine in practice.[29] Finally, after the original publication of VCOG-CTCAE v1.0[20] which was used in this protocol design, the updated v1.1[30] has established a grade 3 AE as > 4× the ULN for ALT and the observed activity would not have been classified as dose limiting under the new guidelines.

In summary, the preponderance of data indicate that paclitaxel (micellar) is active against macroscopic advanced nonresectable MCT in dogs and carries a safety margin consistent with cytotoxic chemotherapeutic class agents. Both activity and safety profile were superior to the lomustine comparator. Exploratory analyses allowed comparison of safety and activity to other currently available treatments, however, more clinically relevant than direct comparisons, the availability of paclitaxel (micellar) with its nonoverlapping mechanisms of action and adverse event profile relative to currently registered TKI, should ultimately lead to investigations of combination treatments, which, as is the current paradigm in medical oncology, may result in more active and durable treatment protocols.

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Conflict of Interest: Dr Vail periodically receives honoraria from Oasmia for his consultancy work in oncology. Dr von Euler is a part-time employee with Oasmia. Drs Rusk's and Khanna's employment and consultancy with Animal Clinical Investigation as the study's Medical Director and Study Coordinator, respectively, were funded as contract research activities by Oasmia.

Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BESTORR	best overall response rate
BORR	biologic observed response rate

CIN	chemotherapy-induced neutropenia
CORR	confirmed overall response rate
CR	complete response
DLT	dose-limiting toxicity
GCP	good clinical practice
GI	gastrointestinal
AE	adverse event
MCT	mast cell tumors
MTD	maximally tolerated dose
PD	progressive disease
PFS	progression-free survival
PR	partial response
SD	stable disease
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VCOG-CTCAE	Veterinary Comparative Oncology Group Common Terminology Criteria for Adverse Events

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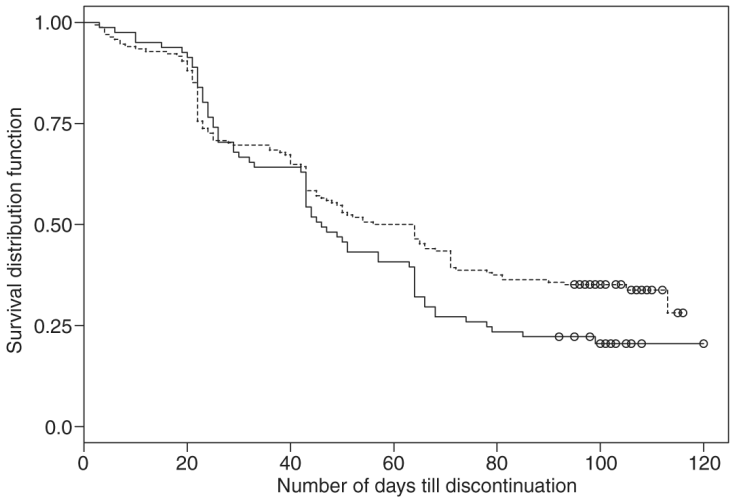

Fig 1.

Kaplan–Meier schematic of dogs discontinuing from the study that received paclitaxel (micellar) [dotted line] or lomustine [solid line]. The *y*-axis represents the proportion of dogs remaining over time (days; *x*-axis). Censored values are indicated with open circles.

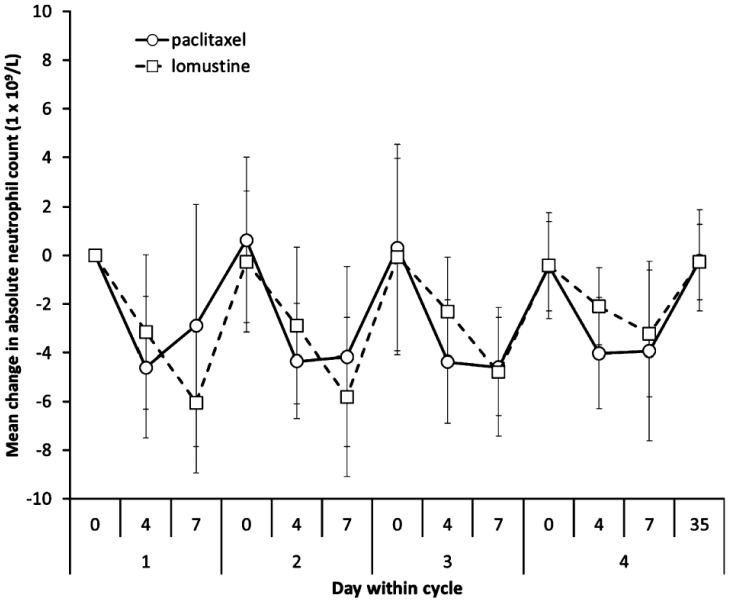

Fig 2.
Mean (± SD) change (from baseline) for neutrophil count over time by treatment group.

Table 1

Study treatment cycles, visits, and days.

Cycle	Cumulative Days	Visit	Day within Cycle
Screening	−14 to −1	V1	
Treatment cycle 1	0	V2	0
		V3	4 ± 1
		V4	7 ± 2
Treatment cycle 2	21	V5	0 ± 3
		V6	4 ± 1
		V7	7 ± 2
Treatment cycle 3	42	V8	0 ± 3
		V9	4 ± 1
		V10	7 ± 2
Treatment cycle 4	63	V11	0 ± 3
		V12	4 ± 1
		V13	7 ± 2
End of study visit	100	V14	35 ± 3

Table 2

Study events by visit.

Event	Visit 1	Visits 2, 5, 8, 11	Visits 3, 6, 9, 12	Visits 4, 7, 10	Visit 13	Visit 14
Owner consent	X					
Demographics, med. history	X					
Concomitant meds.	X	X	X	X	X	X
Phys. exam, vital signs	X	X	X	X	X	X
Target/nontarget lesions	X					
Diagnosis	X					
Tumor grading	X					
Tumor staging	X				X	X
Inclusion/exclusion	X					
Hematology	X	X	X	X	X	X
Clinical chemistry	X	X		X	X	X
Urinalysis	X	X		X	X	X
Performance status score	X	X	X	X	X	X
RECIST[a]		X			X	X
Study drug administration		X[b]				
Adverse event reporting		X	X	X	X	X

[a] Response evaluation criteria in solid tumors (RECIST v1.0). Tumor measurements were made at Visits 5, 8 and 11 to determine progression.

[b] Study drugs administered after all scheduled assessments were made at Visits 2, 5, 8 and 11.

Table 3

Summary of study dog disposition and reason for study discontinuation (n and %).

Disposition	Total	Paclitaxel (Micellar)	Lomustine
Randomized	252	169	83
Treated	249	168	81
Treated with all 4 cycles[a]	90	71 (42%)[*a]	19 (24%)[†]
Completed[a]	76	60 (36%)[*]	16 (20%)[†]
Discontinued (for reason below)	173	108	65
Progressive disease	114	88 (81%)[b]	26 (40%)
Hepatopathy	30	3 (3%)	27 (42%)
Death or euthanasia	16	10 (9%)	6 (9%)
Other adverse event	3	3 (3%)	0
Other reason[c]	10	4 (4%)	6 (9%)

[*,†] Treatments differ significantly ($P < .05$).

[a] With respect to the number of treated dogs.

[b] With respect to the number of discontinued dogs.

[c] Protocol noncompliance, withdrawn owner consent, or reason not recorded.

Table 4

Demographic and baseline characteristics.

Demographic	Category/ Unit	Paclitaxel (Micellar) N = 168	Lomustine N = 81
Sex, n (%)	Male	77 (46%)	33 (41%)
	Female	91 (54%)	48 (59%)
Neutered, n (%)	No	17 (10%)	11 (14%)
	Yes	151 (90%)	70 (86%)
Age, mean ± SD	Months	103 ± 33	106 ± 32
Weight, mean ± SD	Kg	28 ± 13	28 ± 13
Tumor grade, n (%)	2	114 (68%)	56 (69%)
	3	54 (32%)	25 (31%)
Tumor stage, n (%)	1a	1 (1%)	0
	2a	23 (14%)	11 (14%)
	3a	144 (86%)	70 (86%)

Table 5

Summary of overall response rate (n and% of responders) and distribution of RECIST (v1.0) responses.

	Paclitaxel (Micellar) N = 168		Lomustine N = 81	
Responders	***CORR*** *	***BORR (CB)*** ‡	***CORR*** *	***BORR (CB)*** ‡
n (%)	12 (7%)[a]	39 (23%)[c]	1 (1%)[b]	8 (10%)[d]
95% CI	3–11%	17–30	0–4%	3–16%
odds ratio	6.479	3.097		
RECIST (v1.0) overall response				
N	60		16	
complete (CR)	2 (3%)		0	
partial (PR)	10 (17%)		1 (6%)	
stable (SD)	27 (45%)		7 (44%)	
progressive (PD)	21 (35%)		8 (50%)	

*Confirmed Overall Response Rate: Dogs rated by the veterinarian as CR or PR at both Visit 13 and Visit 14 (7 and 35 days, respectively after the 4th treatment cycle).

‡Confirmed Biologic Overall Response Rate (Clinical Benefit): dogs rated by the veterinarian as CR, PR, or SD at both Visit 13 and Visit 14 (7 and 35 days, respectively, after the 4th treatment cycle).

[a,b]Treatments differ significantly ($P < .05$).

[c,d]Treatments differ significantly ($P < .05$).

Table 6

Incidence of dogs with clinically significant adverse events (AE) and those qualifying as severe (VCOG ≥ 3).

	Paclitaxel (Micellar)		Lomustine	
	N = 168		N = 81	
	All AE (%)	VCOG ≥ 3 (%)	All AE (%)	VCOG ≥ 3 (%)
Neutropenia	82	73	93	86
Emesis	79	20	51	6
Hepatopathy	19	5	49	33
Anorexia	76	10	48	1
Diarrhea	70	9	46	4
Lethargy	69	7	47	5
Alopecia	39	3	2	0
Dehydration	26	10	14	7
Dermatitis	24	2	10	0
Pyrexia	13	2	17	7
Edema	14	2	4	1
Lameness	12	5	10	5
Anemia	8	2	6	2
Loss of body condition	7	0	1	0
Thrombocytopenia	7	0	9	2
Leukopenia (nonneutrophil)	4	2	9	5

Table 7

Incidence (%) of dogs with an investigator-rated performance status score of “normal” and owner-observed reports of nausea, vomiting, and diarrhea.

Cycle	**1**			**2**			**3**			**4**			
Days within Cycle	**0**	**4**	**7**	**0**	**4**	**7**	**0**	**4**	**7**	**0**	**4**	**7**	**35**
Normal													
paclitaxel	88	51	72	74	65	77	76	63	70	76	67	71	73
lomustine	89	88	76	86	85	84	86	78	84	81	71	67	61
Nausea													
paclitaxel		75	30	13	53	14	10	45	20	7	50	9	2
lomustine		26	16	13	15	13	6	3	0	0	7	0	5
Vomiting													
paclitaxel		50	5	7	24	5	10	10	1	0	7	0	2
lomustine		12	7	13	2	6	15	7	0	3	0	0	0
Diarrhea													
paclitaxel		27	10	6	22	4	2	15	8	1	12	1	3
lomustine		12	5	9	2	7	2	0	0	0	0	0	10