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Pharmacokinetic study comparing doxorubicin concentrations after chemoembolization or intravenous administration in dogs with naturally occurring nonresectable hepatic carcinoma

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Abstract

Background: Chemoembolization is a viable treatment option for patients with non-resectable hepatic carcinoma (HC) and may allow delivery of chemotherapeutic drugs with decreased systemic toxicity.

Hypothesis/Objective: Compare the serum concentrations of doxorubicin after chemoembolization or IV administration in the same patient. We hypothesized that locoregional delivery may result in increased tumor chemotherapeutic drug concentrations, reflected by decreased measurable serum drug concentrations. Adverse hematological events were hypothesized to be decreased after locoregional delivery.

Animals: Seventeen client-owned dogs with incompletely resectable HC.

Methods: Prospective, single-arm clinical trial. Drug-eluting bead transarterial chemoembolization was performed to varying levels of blood flow stasis (NO STASIS, STASIS). Intravenous doxorubicin (IVC) subsequently was administered in selected patients. Systemic exposure was quantified by area under the serum doxorubicin concentration time curve (AUC), maximum serum doxorubicin concentration (C_{max}), and time doxorubicin was last above the limit of quantitation (T_{last}). Nadir test results after treatments were used to evaluate adverse hematological events.

Results: Thirteen NO STASIS treatments, 15 STASIS treatments, and 9 IVC treatments were performed. Maximum serum doxorubicin concentration, AUC, and T_{last} were significantly lower when comparing NO STASIS or STASIS to IVC treatments. Of the patients with nadir results available, no adverse hematological events were observed after NO STASIS or STASIS treatments. Two patients developed adverse hematological events after IVC treatment.

Conclusions/Clinical Relevance: Drug-eluting bead transarterial chemoembolization offers a viable treatment option for patients with incompletely resectable HC with the potential for increased local tumor doxorubicin concentrations, decreased systemic chemotherapeutic exposure, and fewer adverse hematological events.

KEYWORDS

chemotherapy, hepatic disease, hepatocellular carcinoma, interventional radiology

1 | INTRODUCTION

Massive, solitary hepatocellular carcinoma (HCC) is the most common form of hepatobiliary tumor in dogs.[1-4] Surgical resection is the treatment of choice and, with complete surgical resection of the tumor, median survival times up to 1460 days have been reported.[4] However, when the tumor is nonresectable, treatment options are limited.

In humans, transarterial chemoembolization (TACE) and drug-eluting bead transarterial chemoembolizaton (DEB-TACE) are the standard of care for treatment of nonresectable HCC.[5-9] Transarterial chemoembolization is administered by selective catherization under fluoroscopic guidance to deliver a higher chemotherapeutic drug concentration to the tumor itself, leaving lower chemotherapeutic drug concentrations in the circulation and fewer systemic adverse effects. Benefits of TACE for hepatic carcinoma (HC) in dogs must be explored further, but it may represent a promising palliative treatment option.[10,11]

Drug-eluting bead TACE has been shown to be safe and effective in humans with the advantage of lower bioavailability based on local liver delivery as indicated by lower area under the serum concentration curve (AUC) and lower maximum systemic concentration (C_{max}) as compared to conventional TACE.[12,13] The AUC has been shown to be predictive of myelosuppression for dogs receiving an IV chemotherapy infusion.[14] If DEB-TACE provides increased chemotherapeutic drug concentrations (supra-systemic) within the liver, it also should lead to a decrease in the systemic doxorubicin AUC as compared to IV administration, and potentially decrease systemic toxicity.[15] Our objective was to compare systemic concentrations of doxorubicin after 2 different degrees of chemoembolization vs IV administration. We hypothesized that decreased measurable systemic chemotherapeutic agent concentration would be observed after locoregional delivery. Consequently, adverse hematological events were hypothesized to be decreased compared to those incurred after IV administration.

2 | MATERIALS AND METHODS

2.1 | Case selection

Dogs with nonresectable HC diagnosed between April 2010 to July 2015 were prospectively enrolled in the study. The dogs were treated with 2 different degrees of chemoembolization and IV chemotherapy (IVC), separately, after owner consent. The clinical trial protocol was approved by the Animal Medical Center Institutional Animal Care and Use Committee. Fifteen of 17 dogs were reported in a previous treatment response study.[10]

Inclusion criteria for patients were as follows: mass determined to be nonresectable without considerable risk to the patient if curative intent surgery were to be pursued and histologic or cytologic diagnosis of HC. Exclusion criteria were as follows: surgical intervention other than biopsy within 3 months of the clinical trial, prior chemotherapy, or prior radiation therapy.

Standard techniques for staging were performed within 30 days of the first treatment for the clinical trial, including physical examination, 3-view thoracic radiographs or computed tomography (CT) scan, CBC, serum biochemistry profile, resting bile acid concentrations, urinalysis, and abdominal CT-angiography (CT-A) scan.

2.2 | Procedures

The DEB-TACE procedure was performed as described previously.[10] Dogs enrolled in the study received treatments 6 weeks apart. The first 2 treatments were both DEB-TACE procedures performed to varying levels of blood flow stasis, also given 6 weeks apart. The initial treatment was delivered with the goal of delivering the chemotherapeutic drug-eluting beads into the tumor while maintaining ongoing tumor blood flow and access to the vessel to allow for a subsequent treatment and was referred to as NO STASIS. The second treatment was delivered until blood flow stasis was achieved by the additional delivery of embolic beads without chemotherapeutic drug after the drug-eluting beads in order to provide additional tumor ischemia, and was referred to as STASIS. Both DEB-TACE procedures were performed approximately 6 weeks apart under general anesthesia with arterial access obtained via the femoral or carotid arteries. The chemotherapeutic drug was administered via 100 to 300 μ drug-eluting beads containing 30 mg/m² doxorubicin (1 mg/kg if the patient was <10 kg body weight) after obtaining selective access to the main arterial supply of the tumor via the hepatic arterial branch. For the STASIS treatment, complete embolization with no further tumor perfusion was confirmed by angiography. For patients in which the first treatment resulted in stasis, the treatment was categorized as a STASIS treatment.

Patients that subsequently received IVC (30 mg/m² doxorubicin or 1 mg/kg if <10 kg body weight) received this treatment

approximately 6 weeks after the STASIS procedure. Doxorubicin was administered via a peripheral vein and under general anesthesia during a restaging CT scan. After all 3 treatments (NO STASIS, STASIS, IVC), patients were continued on the same IV fluid therapy regimen for 24 hours until final blood collection.

It was anticipated that patients would be discharged the day after treatment with the following medications: tramadol (2-4 mg/kg PO q8h as needed for pain), omeprazole (1 mg/kg PO q12h for 7-14 days), amoxicillin/clavulanate (13.75 mg/kg PO q12h for 14 days), ondansetron (0.1-1 mg/kg PO q24h for 7 days), and prednisone (1 mg/kg/day PO for 3 days, then 0.5 mg/kg/day PO for 3 days, and then 0.5 mg/kg/day PO q48h for 3 doses). A standard protocol of antiinflammatory drugs, antibiotics, antinausea medications, analgesics, and gastrointestinal protectants is routinely used for treatment of possible postembolization syndrome (PES) based on recommendations for human patients.[10]

2.3 | Sample collection

Two mLs of blood were collected from a peripheral vein before chemotherapeutic drug administration as a control and then at the following time points after administration: 0 hours (immediately after completion of chemotherapeutic drug delivery), 10 min, 30 min, 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours. Samples were sent to the Pennsylvania Animal Diagnostics Laboratory System (PADLS) New Bolton Center Toxicology Laboratory, University of Pennsylvania School of Veterinary Medicine, Kennett Square, Pennsylvania, USA. Analysis was performed by liquid chromatography (Shimadzu, Columbia, Maryland, USA) and triple quad mass spectrometry (API 4000 LC/MS/MS; Sciex; Framingham, Massachusetts, USA). A 0.5 mL aliquot of each serum sample was mixed with 0.25 mL of acetone containing 200 parts per billion (ppb; ng/mL) daunorubicin used as an internal standard (IS) and 0.075 mL of 14% (w/v) zinc sulfate. The mixture was vortexed, filtered, and diluted with 0.225 mL of water before liquid chromatography with tandem mass spectrometry (LC/MS/MS) analysis using an API 4000 triple quadrupole LC/MS/MS. Doxorubicin was analyzed with a mass transition of 544.4/397.1 and daunorubicin (IS) with a mass transition of 528.2/363.1 at 18 V and 22 V collision energy, respectively. Doxorubicin concentrations in the test samples were measured against a calibration curve prepared with serum spiked at 0, 5, 10, 50, 100, and 500 ppb using IS to obtain accurate results. Test sample results were considered acceptable if controls were within 20% of expected results. A method detection limit of 10 ppb (ng/mL) was established using this method.

Noncompartmental pharmacokinetic (PK) analysis was performed to obtain doxorubicin C_{max}, serum doxorubicin concentration AUC, and time doxorubicin was last above the limit of quantitation of 10 ng/mL (T_{last}). Dose normalized results were used. For results below the limit of quantitation (<10 ng/mL), half the limit of quantitation (5 ng/mL) was used for the first instance and all subsequent instances were removed. This method was chosen to demonstrate the difference in overall patient length of exposure because systemic

concentrations of doxorubicin likely continued to decrease with each time point.[16]

Platelet and neutrophil counts were used to evaluate for myelosuppression after each treatment type and graded according to the Veterinary Cooperative Oncology Group common terminology criteria for adverse events (VCOG-CTCAE).[17] In addition, blood test results obtained immediately before IVC treatment were compared to nadir blood test results after IVC to evaluate for decreases that were not considered adverse events according to the VCOG-CTCAE. Blood test results obtained immediately before NO STASIS and STASIS treatments also were compared to nadir blood test results after NO STASIS and STASIS treatments, respectively.

Postembolization syndrome, a commonly described adverse event after DEB-TACE in humans that consists of nausea, fever, fatigue, and abdominal pain,[18,19] was characterized as either occurring or not occurring after NO STASIS or STASIS treatments. In our patient population, diarrhea was included as a clinical sign attributable to PES based on our experience of performing these procedures with and without chemotherapy. Adverse gastrointestinal effects therefore were not evaluated separately because clinical signs overlap with the definition used for PES.

2.4 | Statistical analysis

Baseline descriptive statistics are reported as mean and SD for normally distributed variables and median (interquartile range) for nonnormally distributed variables. The distribution of residuals was assessed using the Kolmogorov Smirnoff formula and visual inspection. Between-groups analyses of baseline variables were performed using analysis of variance (ANOVA) because error residuals were normally distributed. Interaction of categorical clinical covariates was assessed by ANOVA. Analyses for proportions of categorical variables were evaluated using a Chi Square or Fisher's Exact analysis as appropriate. Time to event analyses were carried out in univariate using Kaplan Meier product limit estimates. Analyses were performed using SAS 9.4 (Cary, NC 2016) and $P < .05$ was considered significant.

3 | RESULTS

Seventeen dogs with nonresectable HC diagnosed between April 2010 to July 2015 were prospectively enrolled in the clinical trial.

The mean age of the patients at the time of treatment was 10.8 years (range, 5.8-13.3 years). There were 7 neutered male dogs, 1 intact male dog, and 9 spayed female dogs included in the study. Six of 17 dogs (35%) included in the study were mixed breed dogs. The remaining 11 dogs (65%) were purebred and included 4 Shih Tzus, 2 Labrador Retrievers, 1 German Wirehaired Pointer, 1 Miniature Schnauzer, 1 Beagle, 1 Australian Shepherd, and 1 Pekingese. The mean weight of the dogs at time of treatment was 17.3 kg (range, 6.2-32.2 kg).

A total of 37 treatments were performed with 13 NO STASIS treatments, 15 STASIS treatments, and 9 IV chemotherapy treatments. In dogs that underwent all 3 treatments, the first treatment was NO STASIS, followed by a STASIS treatment. All dogs that underwent IV chemotherapy had it performed as the final procedure. Median survival time from first treatment until death was 337 days.

No significant differences in C_{max}, AUC, or T_{last} were identified when comparing NO STASIS to STASIS treatments ($P = .91$, $P = .64$, $P = .25$, respectively), but all results were lower in the STASIS group (Figures 1-4). The C_{max}, AUC, and T_{last} each were significantly lower however when comparing NO STASIS to IVC treatments ($P < .001$, $P = 0$, $P = .02$, respectively) or STASIS to IVC treatments ($P = 0$, $P = 0$, $P < .001$, respectively; Figures 1-4).
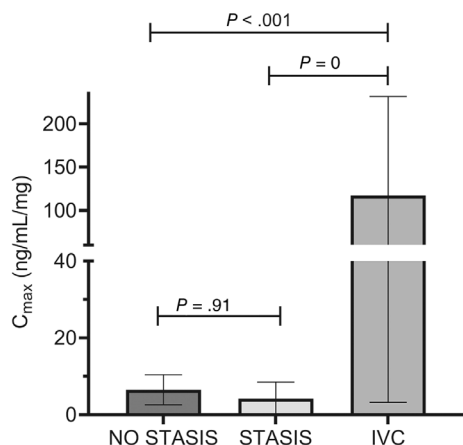

FIGURE 1 Mean dose normalized maximum systemic concentration of doxorubicin by delivery type. Maximum systemic doxorubicin concentration calculated by noncompartmental pharmacokinetic analysis for NO STASIS, STASIS, and intravenous chemotherapy treatment. Bars represent mean values for each delivery type with SD. P values comparing each delivery type provided, with P < .05 considered significant
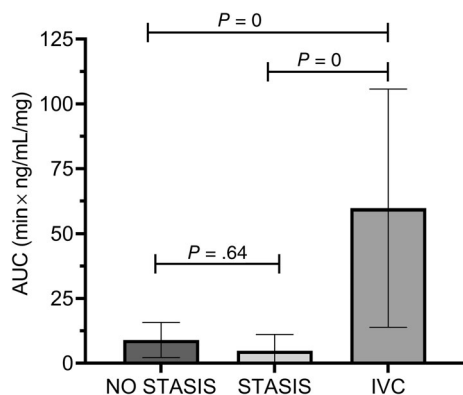
Posttreatment blood tests to evaluate for myelosuppression were obtained between 6 and 16 days after treatment. No significant difference in the timing of posttreatment blood collection was noted after the different treatments.

Ten (10/13; 77%) dogs had nadir blood test results available for evaluation after NO STASIS treatments, 10 of 15 (67%) dogs had nadir blood test results available for evaluation after STASIS treatments, and 6 of 9 (67%) had nadir blood test results available for evaluation after IVC treatments. No adverse hematological events were observed after NO STASIS or STASIS treatments. Two dogs developed adverse hematological events after IVC treatment. One dog (1/6; 17%) developed thrombocytopenia (Grade 1) and neutropenia (Grade 4) after IVC treatment. An additional dog developed neutropenia (Grade 1) after IVC treatment. Therefore, 2 dogs developed neutropenia after IVC treatment (2/6; 33%). The frequency with which adverse hematological events occurred after IVC was significantly higher than for STASIS and NO STASIS treatments ($P = .03$). No significant difference was found between mean neutrophil count after STASIS vs NO STASIS treatments and after NO STASIS vs IVC treatments ($P = .19$, and $P = .14$, respectively). Mean neutrophil count, however, was significantly higher after STASIS treatment compared to IVC treatment ($P = .01$; Figure 5). No significant difference was found between mean platelet count after STASIS vs NO STASIS treatments and after NO STASIS vs IVC treatments ($P = .16$ and $P = .30$, respectively). Mean platelet count however was significantly higher after the STASIS treatment compared to IVC treatment ($P = .03$; Figure 6).

Blood test results obtained pre-IVC treatment were compared to post-IVC nadir results, and no significant difference was found in neutrophil or platelet counts ($P = .56$ and $P = .40$, respectively). Although not statistically significant, a decrease in platelet count occurred in all 6 dogs and a decrease in neutrophil count occurred in 5 of 6 dogs. Blood test results obtained pre-NO STASIS treatment were compared to post-NO STASIS nadir blood test results. No significant difference
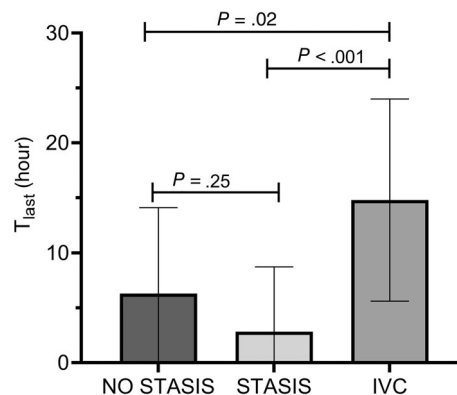

FIGURE 2 Mean dose normalized area under the serum doxorubicin concentration time curve by delivery type. Area under the serum doxorubicin concentration time curve calculated by noncompartmental pharmacokinetic analysis for NO STASIS, STASIS, and intravenous chemotherapy treatment. Bars represent mean values for each delivery type with SD. P-values comparing each delivery type provided with P < .05 considered significant

FIGURE 3 Mean dose normalized time doxorubicin was last above the limit of quantitation of 10 ng/mL by delivery type. Time doxorubicin was last above the limit of quantitation calculated by noncompartmental pharmacokinetic analysis for NO STASIS, STASIS, and intravenous chemotherapy treatment. Bars represent mean values for each delivery type with SD. P-values comparing each delivery type provided, with P < .05 considered significant
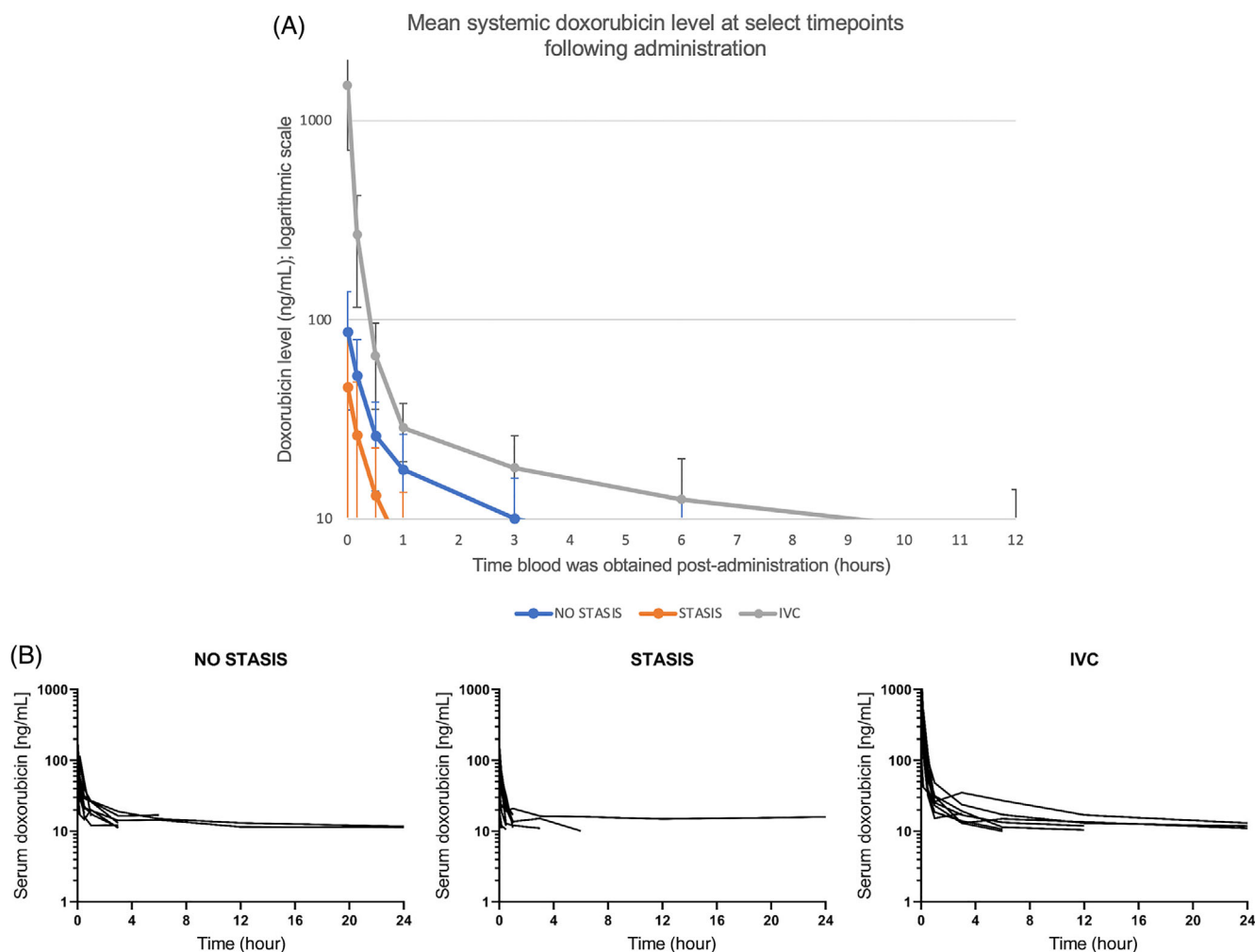
FIGURE 4 (A) Mean systemic doxorubicin concentration at selected timepoints after administration. Peripheral blood samples obtained at specific timepoints (0 hours [immediately after completion of chemotherapy delivery], 10 min, 30 min, 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours) post administration of doxorubicin by 3 different delivery methods (NO STASIS, STASIS, intravenous chemotherapy [IVC]). Doxorubicin (ng/mL) limit of quantitation set at 10 ng/mL (y-axis) and represented by a logarithmic scale. (B) Individual systemic doxorubicin concentration at selected timepoints after administration for each delivery method (NO STASIS, STASIS, IVC). Peripheral blood samples obtained at specific time points (0 hours [immediately after completion of chemotherapy delivery], 10 min, 30 min, 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours) postadministration of doxorubicin. Doxorubicin (ng/mL) limit of quantitation, 10 ng/mL

was found in neutrophil or platelet counts ($P = .10$ and $P = .93$, respectively). Blood test results obtained pre-STASIS treatment were compared to post-STASIS nadir blood test results. A significant difference was found in neutrophil count ($P = .01$) but no significant difference was found in platelet count ($P = .61$).

Clinical signs consistent with PES were reported 10 times (10/28; 36%) after DEB-TACE procedures in 7 of 17 (41%) dogs; 3 experienced PES after both NO STASIS and STASIS treatments. Dogs that experienced PES after NO STASIS or STASIS treatments had no significant differences in C_{max} or AUC when compared to dogs that did not experience PES. Although not statistically significant, the reported mean values for C_{max} and AUC for STASIS and AUC for NO STASIS were higher in those patients that experienced PES than in those that did not.

4 | DISCUSSION

We examined several variables, including C_{max}, AUC, and T_{last} after 3 different methods of chemotherapeutic drug administration: NO STASIS DEB-TACE, STASIS DEB-TACE, and IVC treatments. We found no significant differences between NO STASIS and STASIS treatments with regard to any of these variables, although C_{max}, AUC, and T_{last} were lower in the STASIS patients. Significant differences in C_{max}, AUC, and T_{last} were found between DEB-TACE and IVC treatments, indicating that systemic doxorubicin concentrations were higher when administered IV (NO STASIS vs IVC $P < .001$, $P = 0$, and $P = .02$, respectively; STASIS vs IVC treatments $P = 0$, $P = 0$, $P < .001$, respectively). Given that dose-normalized results were used for comparison, extrapolation of this data suggests that a lower
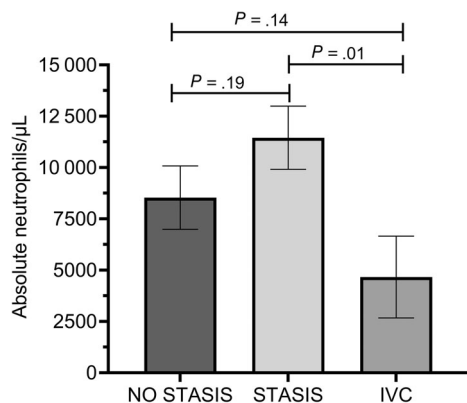
FIGURE 5 Mean posttreatment neutrophil count by delivery type. Bars represent mean values for each delivery type with SD. Absolute neutrophils/µL obtained from posttreatment nadir blood test results. *P*-values comparing each delivery type provided with *P* < .05 considered significant
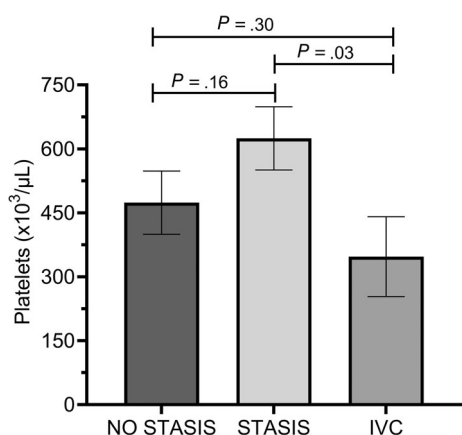

FIGURE 6 Mean posttreatment platelet count by delivery type. Bars represent mean values for each delivery type with SD. Platelets thousands/µL obtained from posttreatment nadir blood test results. *P* values comparing each delivery type provided with *P* < .05 considered significant

systemic concentration indicates the tumor concentration of doxorubicin may be higher when the chemotherapeutic drug is administered via DEB-TACE. Chemotherapy uptake by the tumor is a complex process affected not only by route of administration, but by other factors such as tumor blood supply, rate of metabolism, and rate of elimination.[20-22] Because it is multifactorial, tumor chemotherapy uptake likely will vary among patients. However, regardless of whether tumor doxorubicin concentration is higher, if the systemic concentration is lower, less toxicity and fewer adverse events may occur after regional delivery.

Studies in human patients indicate that conventional TACE results in a similar number of or more adverse events after treatment as compared to DEB-TACE, which was the method for chemoembolization used in our study.[23,24] Drug-eluting bead TACE employs embolic beads that elute chemotherapeutic drugs, such as doxorubicin, over time to increase the amount of time that the drug comes into contact

with the tumor and decrease toxicity from systemic exposure.[8,25] Common adverse effects after systemic administration of doxorubicin that prevent dose escalation include myelosuppression, gastrointestinal signs (eg, nausea, vomiting, diarrhea), and cardiotoxicity.[26] As mentioned previously, the AUC has been shown to be predictive of myelosuppression for dogs receiving IVC.[14] In our study, myelosuppression was determined by evaluating neutrophil and platelet counts on nadir blood tests after administration of chemotherapy. Although blood test results were not obtained on the same day posttreatment for each patient, no significant differences were found between these times. This finding, however, may not be clinically relevant, and blood test timing therefore may have had an impact on our results. The time period after treatment for blood testing ranged from 6 to 16 days, and the nadir for doxorubicin generally is seen at 7 to 10 days after administration.[27] Interestingly, 33% (2/6) of dogs had adverse hematological events after IVC, whereas none did after DEB-TACE, suggesting decreased myelosuppression after locoregional delivery. The frequency with which these adverse events occurred after IVC compared to STASIS and NO STASIS treatments was significant (*P* = .03).

No significant differences were found between NO STASIS and STASIS treatments or between NO STASIS and IVC treatments for platelet and neutrophil counts. However, a significant difference was seen between STASIS and IVC treatments. This observation could be explained by the subsequent inflammatory response and increased neutrophil count seen after liver embolization in the STASIS group, rather than a decreased neutrophil count in the IVC group. In order to further evaluate this concern, pre-IVC blood test results were compared to post-IVC nadir blood test results to determine if decreases in neutrophil and platelet counts occurred after treatment, albeit not substantial enough to be classified as an adverse event. Although not statistically significant, a decrease occurred in platelet count in all 6 dogs after IVC and a decrease in neutrophil count occurred in 5 of 6 dogs in which blood test results were available for comparison.

Pre-NO STASIS and pre-STASIS blood test results were compared to NO STASIS and STASIS nadir blood test results, respectively. The only significant difference found was between pre-STASIS and STASIS neutrophil count, with an increase seen on the posttreatment nadir blood test results. This finding may be explained by the inflammatory response seen after embolization to stasis. The ability to generate a neutrophilic response also suggests that the bone marrow was not substantially affected by delivery of the chemotherapeutic drug.

Although adverse gastrointestinal events were not investigated in our study because of the overlap in clinical signs with PES, they deserve further scrutiny in future studies. In humans, PES generally is considered to occur within the first 24 hours after treatment and has been reported to last up to 2 weeks. It is thought to result from tissue ischemia and subsequent inflammatory cytokine release after DEB-TACE.[28] Diarrhea is only seen in approximately 1.6% of human patients after DEB-TACE procedures.[29] For the purposes of our study, diarrhea was included as a clinical sign of PES as opposed to an adverse gastrointestinal event based on our experience with TAE/TACE in dogs.[10] Adverse gastrointestinal effects generally are seen between 2 and 5 days after administration and result from

gastric and intestinal mucosal inflammation.[30] Therefore, both the clinical signs and time period in which they occur posttreatment often overlap. Additionally, the dogs in our study were discharged on antinausea and antacid medications, which could have further complicated interpretation of the adverse gastrointestinal effects. Additionally, systemic doxorubicin concentrations after TACE procedures were substantially lower than those after IVC treatments. Given that diarrhea was uncommonly seen after IVC treatment where systemic doxorubicin concentrations were higher, it is unlikely that chemotherapy was responsible for causing diarrhea post-TACE in these patients.

No significant differences in AUC or C_{max} were found between dogs that did or did not experience PES after STASIS and NO STASIS treatments, suggesting that level of chemotherapeutic drug exposure may not influence development of PES. Although not statistically significant, for STASIS treatments, the mean values for both AUC and C_{max} were higher in dogs that experienced PES. In people, PES has been shown to develop in up to 86% of patients,[17] which is considerably higher than the 36% (10/28) of dogs in our study population. Postembolization syndrome in humans also has been associated with increased risk of death.[31] In dogs, an association has not yet been shown between PES and death.[10] Because PES can result in increased morbidity and prolonged hospitalization, further investigation of this syndrome in dogs is warranted.

Limitations of our study include the lack of a negative control group and variability in the treatment protocol. Because of the nature of the interventions, there was a lack of randomization in treatment order, which may have affected results. The time for which drug-eluting beads elute doxorubicin is unknown, but a previous study reported that the half-life of 100 to 300 μ drug-eluting beads loaded with 25 mg/mL of doxorubicin had a half-life of 150 hours.[32] This observation suggests that continued release of doxorubicin beyond the 24 hours evaluated in our study is possible. Sample size was small, particularly in regard to the patient group that received all 3 treatments and patients that had posttreatment blood test results available for review. In general, if statistical significance is observed, inadequate sample size should not have been a problem. However, when performing post-hoc power analysis, inadequate power was found when comparing differences in blood cell count nadirs. Post-hoc power analysis suggested that with an alpha of 0.05 and beta of 0.8, group sizes of 43, 18, 35, and 41 would have been required for neutrophil, platelet, STASIS, NO STASIS, IV/NO STASIS, respectively, in order to achieve statistical significance. Central to our study is the idea that lower systemic exposure is a byproduct of increased tumor exposure using DEB-TACE delivery methods. However, increased tumor exposure is only 1 potential cause. It is also possible that delivery of the chemotherapeutic drug directly to the eliminating organ (liver) plays a role in decreased serum doxorubicin concentrations. Without measuring tumor concentrations directly, which is not practical in client-owned patients, increased tumor exposure as a mechanism decreasing systemic concentrations is presumptive, but plausible.

Our study suggests that locoregional delivery results in increased tumor chemotherapeutic drug concentrations as indicated by decreased measurable serum chemotherapeutic drug concentrations. No adverse hematological events occurred after DEB-TACE

treatments, whereas 2 dogs developed them after IVC treatment (33%). Adverse gastrointestinal events were not evaluated because of the overlap with PES, but evaluation of adverse gastrointestinal events after DEB-TACE vs IVC treatments should be evaluated in future studies given the absence of adverse hematological events after DEB-TACE in our study. Fewer adverse events after regional drug delivery could permit supra-systemic chemotherapeutic drug doses to be delivered regionally in the future.

CONFLICT OF INTEREST DECLARATION

Dr. Weisse and Dr. Berent are consultants for Infiniti Medical, LLC. In addition, Dr Weisse is a minority equity holder of this same company. No other authors have a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The clinical trial protocol was approved by the Animal Medical Center Authors IACUC.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.