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Early Tumor Response to Intraarterial or Intravenous Administration of Carboplatin to Treat Naturally Occurring Lower Urinary Tract Carcinoma in Dogs

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Background: Survival times and tumor responses associated with malignant neoplasia of the lower urinary tract are poor despite the vast array of current treatments. Therefore, the evaluation of alternative treatments, such as intraarterial administration of chemotherapy (IAC) should be considered.

Objective: To describe a technique for superselective catheterization for IAC and to evaluate initial tumor response by ultrasonography after both IAC and intravenous administration of chemotherapy (IVC).

Animals: Client-owned dogs with lower urinary tract neoplasia treated with either IVC (n = 15) or IAC (n = 11).

Methods: Retrospective study. An arterial approach via the carotid or femoral artery was utilized to obtain superselective access and administer chemotherapy in the IAC cases. Medical record review was performed, data were recorded, and recorded variables were evaluated statistically.

Results: Intraarterial chemotherapy was successfully administered in all cases. There was a significantly greater decrease in longest unidimensional measurement in the IAC group as compared to the IVC group (P = .013). The IAC group was also significantly more likely to have a tumor response as assessed by modified RECIST guidelines (P = .049). Dogs in the IAC group were significantly less likely to develop anemia (P = .001), lethargy (P = .010) and anorexia (P = .024).

Conclusion and Clinical Importance: This study demonstrated the feasibility and efficacy of performing IAC for lower urinary tract neoplasia. Further investigation is necessary as the follow-up time was short and the impact on long-term outcome and survival was not determined.

Key words: Chemotherapy; Transitional cell carcinoma.

Malignant neoplasia of the lower urinary tract of dogs generally carries a poor prognosis. Carcinomas are the most common neoplasm affecting the urinary bladder, urethra and prostate of dogs, and the majority of these tumors are urothelial in origin, with the predominant subtype being transitional cell carcinomas (TCC).[1,2] Traditional treatments include surgery, nonsteroidal anti-inflammatory drugs, chemotherapy, radiotherapy, or a combination of these modalities.[2–8] The results from such treatments have been mixed. In most practices, chemotherapy administered IV in conjunction with an oral nonsteroidal anti-inflammatory drug (NSAID) is the pursued treatment. Mitoxantrone, cisplatin, carboplatin, chlorambucil, doxorubicin, actinomycin D, and vinblastine have antitumor activity against urinary bladder and urethral TCC; however, tumor responses are typically incomplete and short-lasting. Median survival times have differed depending on the protocol utilized but are generally <1 year.[3,4,7,9–15]

Nonsteroidal anti-inflammatory drugs administered either alone or in combination with chemotherapy are commonly used in the treatment of TCC.[16–18] Tumor regressions occurred in 6 of 34 dogs treated with piroxicam as a single agent, and 2 of these cases had complete and durable remissions while on treatment.[16] The response to NSAIDs has been confirmed by several follow-up studies.[4,7,17,19] As only complete responses (CRs) are likely to significantly prolong remission and survival in cancer patients, the activity of NSAIDs in canine TCC has received significant attention.

An alternative to the traditional intravenous administration of chemotherapy is the intraarterial administration of chemotherapy. In humans, the use of intraarterial chemotherapy (IAC) is expanding. In these cases, arterial access is obtained and fluoroscopic guidance is utilized to achieve superselective catheter placement within the arterial supply of a tumor. The goal of

Abbreviations:

CR	complete response
IAC	intraarterial chemotherapy
IVC	intravenous chemotherapy
PD	progressive disease
TCC	transitional cell carcinomas

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Work completed at the Interventional Radiology and Oncology clinics at the University of Pennsylvania, School of Veterinary Medicine and the Animal Medical Center, Interventional Radiology Service.

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IAC delivery is to increase the local (and subsequently intratumoral) concentration of chemotherapy, decrease systemic adverse effects, and potentially generate a greater tumor response.[20]

The use of IAC for the treatment of urinary bladder TCC has been described in 2 dogs.[21] In those dogs, arterial access was obtained via the carotid artery and IAC (cisplatin) was administered at the level of the external iliac arteries; radiotherapy was also administered to potentially generate an improved response with the combined therapy. In those dogs, minimal adverse effects were noted and the procedure was performed without incident.[21] Some of the dogs in the IAC treatment group in the current report were also included in an abstract describing the technique and repeatability of superselective IAC in dogs with urothelial tumors.[22] In those cases, 22 dogs received up to 6 treatments each, often in terminal arteries, and complications were uncommon and typically minor.[22]

As survival times and tumor responses remain poor despite the vast array of surgery, radiotherapy and chemotherapy protocols utilized in the treatment of neoplasia affecting the lower urinary tract, evaluation of alternative treatments is necessary. The primary goal of this study was to describe a technique for superselective catheterization of the arterial blood supply to the urinary bladder, urethra, and prostate for the specific purpose of intraarterial administration of chemotherapy and NSAIDs. A secondary goal was to compare initial tumor response (before treatment and subsequent ultrasonography evaluation) after IA administration of carboplatin in 1 group of dogs to initial tumor response after IVC in a different cohort of dogs. Initial tumor response was defined as the change in tumor size from the ultrasound evaluation before treatment to the ultrasound evaluation after treatment. We hypothesized that a technique of superselection of arteries supplying the lower urinary tract of dogs would be feasible, safe, and repeatable, and there would be a greater decrease in tumor size after IAC than IVC utilizing carboplatin.

Materials and Methods

Criteria for Selection of Cases

A retrospective, multi-institutional study was performed. The databases of the Interventional Radiology and Oncology clinics at the University of Pennsylvania School of Veterinary Medicine (2007–2009) and the Animal Medical Center Interventional Radiology Service (2009) were searched for dogs with neoplasia (carcinoma) of the urinary bladder, urethra, or prostate that were treated by IAC or IVC administration. Dogs were included in the IAC group if a cytologic or histologic diagnosis of carcinoma was obtained, and carboplatin and an NSAID were administered via artery by a single operator. Dogs were included in the IVC group if a cytologic or histologic diagnosis of carcinoma was obtained, and a protocol of intravenous carboplatin and an oral NSAID was administered under the supervision of a board-certified veterinary oncologist during the same time period as the IAC group; dogs receiving other chemotherapy drugs were excluded. No dog in either group had received previous treatment with an NSAID, chemotherapy, or radiation therapy.

Procedures

Medical record review was performed and data recorded from the medical record included: signalment (age, breed, and sex), weight, diagnostic imaging findings (radiography and ultrasonography), and IAC procedural findings. Additionally, the adverse events/complications were noted after each chemotherapy treatment and recorded according to published VCOG-CTCAE guidelines.[23]

Vascular Selection: Carotid Artery. All dogs were placed in dorsal recumbency and the ventral and lateral cervical neck regions were clipped and prepared with sterile technique. A 2–4 cm incision was made between the trachea and jugular vein on the left or right side. The subcutaneous tissues were bluntly and sharply dissected until the carotid arterial pulse could be palpated. The fascia surrounding the carotid sheath was gently dissected to allow clear visualization and isolation of the carotid artery. Two lengths of 3-0 polydioxanone[a] suture were placed around the exposed region of the carotid artery. The cranial polydioxanone suture was ligated around the carotid artery. An 18-gauge over-the-needle catheter[b] was introduced into the carotid artery and the needle was removed. An 0.035-inch hydrophilic guide wire[c] was introduced into the catheter and subsequently into the carotid artery. The catheter was removed over the guide wire. A 4-6 Fr vascular access sheath and dilator[d] were introduced into the carotid artery over the guide wire, and the caudal polydioxanone suture was left in place loosely. The sheath was sutured to the skin and the dilator was removed over the guide wire.

The fluoroscopy unit was then positioned over the dog. A 4 Fr Berenstein catheter[e] was introduced into the vascular access sheath over the guide wire and the guide wire-catheter combination was passed from the carotid artery into the thoracic aorta and further into the abdominal aorta to the level of the caudal aorta (Fig 1). The guide wire was then removed from the vascular access sheath. A 50% saline/50% contrast[f] mixture was drawn into a syringe and attached to the Berenstein catheter, and approximately 5 mL was injected under fluoroscopic guidance to delineate the vascular anatomy of the terminal aorta (Fig 1).

Vascular Selection: Femoral Artery. All dogs were placed in dorsal recumbency and the inguinal region was clipped and prepared with sterile technique. The right or left femoral artery was digitally palpated through the skin, and a 2 cm incision over the femoral artery was made. The fascia surrounding the femoral artery was dissected allowing clear visualization of the femoral artery. Two lengths of 3-0 polydioxanone[a] suture were placed around the exposed region of the femoral artery. The distal polydioxanone suture was ligated around the femoral artery. An 18-gauge over-the-needle catheter was introduced into the femoral artery and the needle was removed. An 0.035-inch hydrophilic guide wire was introduced into the catheter and subsequently into the femoral artery. The catheter was removed over the guide wire. A 4-6 Fr vascular access sheath and dilator were introduced into the femoral artery over the guide wire and the proximal polydioxanone suture was left in place loosely. The sheath was sutured to the skin and the dilator was removed over the guide wire.

The fluoroscopy unit was then positioned over the caudal abdomen of the patient. The guide wire was passed from the femoral artery and into the ipsilateral external iliac artery. A 4 Fr Cobra[g] catheter was then placed into the vascular access sheath over the guide wire. Using the guide wire and Cobra catheter combination, the contralateral external iliac artery was selected. The Cobra catheter was then removed over the wire and replaced with a 4Fr reverse curve catheter[h] . The catheters were then manipulated into the terminal aorta at the level of the internal iliac arteries. The guide wire was then removed and a 50% saline/50% contrast mixture was drawn into a syringe that was attached to the catheter

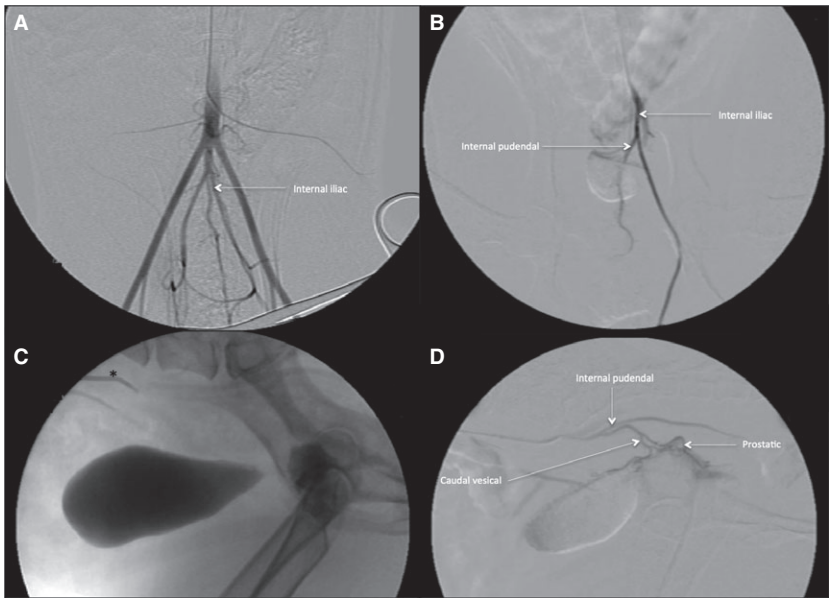

Fig 1. Fluoroscopic images during an intraarterial chemotherapy procedure for the treatment of a prostatic carcinoma. (**A**) A contrast injection with digital subtraction has been performed at the level of the caudal aorta, and the arteries of the aortic trifurcation can be visualized. (**B**) The Berenstein catheter has been advanced into the internal iliac artery, and the internal pudendal artery can now be visualized during this subtracted contrast injection. (**C**) The dog has been repositioned into lateral recumbency, and the Berenstein catheter (*) can be visualized at the origin of the internal pudendal artery. (**D**) The arteries that are selected during superselection of the prostatic artery can be visualized in this subtracted image.

and approximately 5 mL was injected under fluoroscopic guidance to delineate the vascular anatomy of the terminal aorta.

Intraarterial Chemotherapy Administration. Superselection of the terminal arteries was attempted in all cases. To perform superselection, a microwire (0.014-inch)[i] and microcatheter (1.8–2.4 Fr)[j] combination was used to access the internal iliac artery and subsequently the internal pudendal artery (Fig 1). The microwire was then removed, and the patient was moved into lateral recumbency to allow for better visualization of the terminal arteries. Once in lateral recumbency, an injection of 100% contrast was performed to delineate the arterial supply to the tumor and the terminal arteries. The microwire was reintroduced into the microcatheter and the combination was utilized to select the most terminal artery (prostatic, vaginal, or caudal vesical).

Before chemotherapy administration, a separate sterile surgical table was established, and all individuals in the catheterization laboratory donned appropriate protective gear including goggles and powder-free gloves. Chemotherapy (carboplatin) and meloxicam were placed onto the surgical table with sterile technique. The systemic dose of carboplatin was utilized in all cases; 250 mg/m^2 was administered at the 1st treatment, and if this was tolerated, the dose was increased to 275 mg/m^2 at the 2nd dose. The dose of meloxicam administered intraarterially was between 0.1 and 0.2 mg/kg; the lower dose was chosen in dogs with a previous history of gastrointestinal upset or poor tolerance of NSAIDs. Undiluted chemotherapy was mixed with contrast 1:1 to allow for visualization during administration to limit reflux of chemotherapy into more proximal arteries; half of the chemotherapy administration was performed via 1 mL syringes attached to the microcatheter on 1 side. After chemotherapy administration, the microcatheter was flushed with saline and then half of the meloxicam dose was administered mixed 1:1 with contrast as well. Once injection was complete, the microcatheter was flushed with saline and a repeat arteriogram was performed to confirm blood flow to the area and document any evidence of thrombosis or extravasation. After the treatment of 1 side of the lower urinary tract with half of the chemotherapy and meloxicam dose, the patient was moved into dorsal recumbency again. The Cobra catheter and microcatheter combination were withdrawn slowly to the level of the internal iliac arteries and vascular selection was performed on the contralateral side allowing for administration of the remaining half of the chemotherapy and meloxicam dose in the same manner as described above.

After completion of IAC administration, the instrumentation was removed, and the artery was ligated. The subcutaneous tissue and skin were closed with 3-0 poliglecaprone[k] in 2 layers. In total, 2 full doses of IAC were administered 3 weeks apart, and abdominal ultrasonographic evaluation of the tumor was performed after the first 2 treatments. The total dose of contrast administered did not exceed 2 mL/kg in any dog.

Imaging, Tumor Measurement, and Endpoints for Comparisons. An abdominal ultrasonographic examination was performed before treatment in all dogs (IAC and IVC groups) and after 2 treatments (IAC group) or 2–3 treatments (IVC group) had been administered. The response comparison endpoint between the 2 treatment groups was the after treatment ultrasound. For this study, a single board-certified radiologist retrospectively reviewed all ultrasonographic examination images and recorded the following tumor parameters on the before treatment and first after treatment ultrasonographic examination: the longest diameter length, width, and height, from which the estimated tumor volume was ultimately calculated. When archived ultrasound images only included 1 imaging plane (ie, sagittal plane), bidimensional measurements were obtained but estimated tumor volume could not be calculated. The percentage change in tumor length, width, height, and volume were calculated. To determine tumor response, a modification of the RECIST guidelines was utilized based upon the longest unidimensional ultrasonography measurement (rather than the originally described computed tomography or caliper measurements)[24]; briefly, when comparing the first to second ultrasonography assessment, a CR was considered the disappearance of the lesion, a PR was considered at least a 30% decrease in the tar-

get lesion diameter, progressive disease (PD) was considered at least a 20% increase in the target lesion diameter, and stable disease (SD) was considered a lesion that demonstrated neither sufficient regression to be considered a PR nor sufficient growth to be considered PD. A specific protocol to fill the bladder with a consistent amount of fluid before ultrasound was not followed.

Statistical Analysis

The changes in length, height, width, and volume and the percentage change in length, height, width, and volume were compared between the IAC and the IVC groups using an exact Wilcoxon-Mann–Whitney test. Additionally, the change in the longest unidimensional measurement and the percentage change in the longest unidimensional measurement were compared between the IAC and the IVC groups, as were the modified RECIST responses in each group, using an exact Wilcoxon-Mann–Whitney test. Before and after treatment, paired data were analyzed with an exact Wilcoxon signed rank test. Dichotomous variables were compared between the IAC and the IVC groups using Fisher's exact test. P-values $\leq .05$ were considered statistically significant.

Results

Intraarterial Chemotherapy Subgroup

Eleven dogs met inclusion criteria in the IAC cohort. The median age of the dogs receiving IAC was 11 years (range, 6.5–13 years). Breeds represented included Bassett Hound (1), Bearded Collie (1), Bichon Frise (1), Lhasa Apso (1), Pembroke Welsh Corgi (1), Samoyed (1), Scottish Terrier (1), Shih Tzu (1), and Yorkshire Terrier (1); additionally, 2 dogs were considered mixed breed. There were 8 female spayed and 3 male castrated dogs included in this group. The median weight of the dogs enrolled in the group was 16 kg (range, 5.8–31 kg).

Thoracic radiography (3-view) was performed prior to IAC administration in all cases. Eight dogs were noted to have normal thoracic radiographs. Abnormalities on thoracic radiographs included suspected pulmonary parenchymal metastatic disease (n = 3), mildly enlarged heart (2), suspected rib metastasis (1), and suspected dorsal spinous process metastasis (1). Abdominal ultrasonography results were available for all dogs. A mass or masses was noted in the bladder/urethra (n = 8) or prostate (3) in all dogs. A diagnosis was obtained in all cases and included transitional cell carcinoma (n = 8) and prostatic carcinoma (3).

The carotid artery was utilized for vascular access in 9 dogs, and the femoral artery was used for access in 2 dogs. Anesthesia and procedural times were available in 8 cases (17/22) procedures. The median total anesthesia time during the IAC administration was 150 minutes (range, 80–220 minutes) and the median IAC procedural time was 70 minutes (range, 35–135 minutes). The intraprocedural complications included hemorrhage from a secondary peripheral arterial line (n = 1) and a unilateral delivery of the full-dose chemotherapy (1). No bleeding complications at the vascular access site were noted, and all cases were considered technical successes in that catheters were able to be positioned in the blood vessel of choice and chemotherapy was administered successfully. After procedure complications included mild lameness in 2 dogs that had undergone femoral arterial access. One dog that required bilateral carotid artery ligation had temporary blindness and disorientation, likely secondary to an ischemic event. The adverse events associated with IAC administration included 8 neutropenic episodes (7 grade 1 and 1 grade 2) and 2 episodes of diarrhea (grade 1).

All dogs had ultrasonographic evaluation of the tumor before treatment and again after 2 treatments (approximately 3 weeks after the second treatment). The tumor measurements and percentage changes are recorded in Table 1. When utilizing the modified RECIST guidelines described in this study, 4 dogs had a PR, and 7 dogs demonstrated SD when comparing the first and second ultrasonography assessments. No dogs had PD.

There was a significant decrease in tumor length ($P = .002$), width ($P = .031$), and height ($P = .015$) when comparing the before treatment ultrasonography measurements to the after treatment ultrasonography measurements. Additionally, there was a significant difference when comparing the before treatment longest unidimensional measurement to the after treatment longest unidimensional measurement ($P = .001$).

Intravenous Chemotherapy Subgroup

Fifteen dogs met inclusion criteria in the IVC cohort. The median age of the dogs receiving IVC was 11 years (range, 8.5–13.5 years). Breeds represented included Beagle (n = 2), Labrador retriever (1), Lhasa Apso (1), Maltese (1), Rat Terrier (1), Scottish Terrier (1), Soft-coated Wheaten Terrier (1), and West Highland White Terrier (1); 6 dogs were considered mixed breed. There were 7 female spayed, 7 male castrated dogs and 1 intact male dog included in this group. The median weight of the dogs enrolled in the group was 15.6 kg (range, 8.6–41.9 kg).

Thoracic radiography (3-view) was performed before IVC administration in all cases. Fourteen dogs were noted to have no abnormal findings on thoracic radiographs. Suspected pulmonary metastasis was noted in 1 dog. Abdominal ultrasonography examination results were available in all dogs. One or more masses were noted in the bladder/urethra (n = 14) or prostate (1) in all dogs. A diagnosis was confirmed as TCC in all 15 cases.

A total of 44 IVC administrations were performed in these 15 dogs; 14 dogs received 3 treatments, and 1 dog received 2 treatments. The dose of carboplatin varied between 250 and 300 mg/m^2. Ten dogs received piroxicam (0.2–0.3 mg/kg, PO, q24 hour), 2 dogs received firocoxib (4.7–4.9 mg/kg, PO, q24 hour), 1 dog received carprofen (2.5 mg/kg, PO, q12 hour), 1 dog received deracoxib (1.8 mg/kg, PO q24 hour), and 1 dog received meloxicam (0.1 mg/kg, PO, q24 hour). The adverse events associated with IVC administration included anemia after 18 individual treatments (16 grade 1, 2 grade 2), neutropenia after 22 treatments (13 grade 1, 7 grade 2, 1 grade 3, 1 grade 4), thrombocyto-

Table 1. Tumor size measurements and comparisons between the IAC and IVC groups.

	IAC		IVC			
	Before (a) Median (range)	After (b) Median (range)	Before (c) Median (range)	After (d) Median (range)	*P*-Value a versus c	*P*-Value b versus d
Longest unidimensional measurement	31.5 mm (21 to 87.4 mm)	24.1 mm (0 to 47.9 mm)	33.6 mm (15.9 to 74.9 mm)	36.3 mm (14.4 to 84.2 mm)	.64	.11
Change in length		−7.8 mm (−0.7 to −39.5 mm)		1.3 mm (22 to −16.8 mm)		.013*
Change in width		−3.4 mm (−2.3 to −11 mm)		−0.8 mm (21.7 to −8.1 mm)		.094
Change in height		−2.2 mm (2.3 to −26.7 mm)		−0.1 mm (12.2 to −10.6 mm)		.098
Change in volume		−1847.9 mm^3 (−1507 to −48350.7 mm^3)		1358.9 mm^3 (38039.9 to −18732.5 mm^3)		.364
Change in length percentage		−20.1% (−1.8 to −42.2%)		3.9% (86.3 to −44.6%)		.016*
Change in width percentage		−26.2% (−11.6 to 32.6%)		−3.5% (281.8 to −58.7%)		.018*
Change in height percentage		−16% (17.7 to −66.1%)		0.4% (69.7 to −68%)		.075
Change in volume percentage		−42.1% (−22.7 to −80.8%)		−8.6% (1107 to −88%)		.083
Change in longest unidimensional measurement		−7.8 mm (−0.7 to −39.5 mm)		1.3 mm (22 to −16.8 mm)		.013*
Change in longest unidimensional measurement percentage		−20.1% (−1.8 to −45.2%)		3.9% (86.3 to −44.6%)		.016*

IAC, intraarterial chemotherapy; IVC, intravenous chemotherapy. *Statistically significant.

penia after 6 treatments (3 grade 1, 1 grade 2, 2 grade 3), lethargy after 10 treatments (10 grade 1), anorexia after 10 treatments (6 grade 1, 4 grade 2), and diarrhea after 8 treatments (6 grade 1, 2 grade 2).

All 15 dogs had 2 ultrasonography examinations of the tumor with the first occurring before IVC treatment, and the second occurring after 3 treatments in 14 dogs and after 2 treatments in 1 dog (approximately 3 weeks after the last treatment). The tumor measurements and percentage changes can be found in Table 1. When utilizing the modified RECIST guidelines described in this study, 2 dogs demonstrated a PR, 9 dogs demonstrated SD, and 4 dogs demonstrated PD when comparing the first and second ultrasonography assessments.

There was no significant decrease in tumor length ($P = .525$), width ($P = .496$), and height ($P = .867$) when comparing the ultrasonography measurements before and after treatment. Additionally, there was not a significant difference when comparing the longest unidimensional measurement before and after treatment ($P = .52$).

Comparison Between Intraarterial and Intravenous Groups

There was no significant difference between the IAC and IVC groups for age ($P = .89$), weight ($P = .34$), and sex ($P = .82$). The *P* values for comparison between the IAC and IVC groups can be found in Table 1. There was no significant difference in the before treatment height ($P = .07$), length ($P = .78$), width ($P = .31$), volume ($P = .18$), and longest unidimensional measurement ($P = .64$) when comparing the IAC and IVC groups. There was a significantly greater decrease in tumor length, length percentage, width percentage, longest unidimensional measurement, and longest unidimensional measurement percentage after treatment in the IAC group as compared to the IVC group. The IAC group was significantly more likely to have a tumor response as assessed by modified RECIST guidelines when compared to the IVC group ($P = .049$); eg, 4 of 11 (36%) in the IAC group had a PR, compared to 2 of 15 (13%) in the IVC group.

The development of adverse events was compared between the 2 groups. There was no significant difference in the development of neutropenia ($P = .109$), thrombocytopenia ($P = .053$), diarrhea ($P = .356$), and vomiting ($P = .491$). Dogs in the IAC group were significantly less likely to develop anemia ($P = .001$), lethargy ($P = .010$), and anorexia ($P = .024$).

Discussion

The results of this study demonstrate that IAC for the treatment of lower urinary tract neoplasia can be performed successfully and with minimal complications. Additionally, early tumor response is encouraging as the IAC group demonstrated a significantly greater decrease in tumor length, length and width percentage, longest unidimensional measurement, and longest unidimensional measurement percentage as compared to the

IVC group when using carboplatin and NSAID chemotherapy protocols. The IAC group was also significantly more likely to demonstrate a tumor response as evaluated with the modified RECIST guidelines described in this study.

The IAC administration procedure is technically challenging, and requires a strong understanding of the vascular anatomy. Additionally, as the arterial system is being accessed, it is important to be cognizant of the placement of instrumentation and the potential loss of blood that can occur with these arterial procedures. Similar chemotherapy safety protocols to what are utilized for IVC administration should be instituted for IAC administration, and all members of the treatment team should take proper precautions. Complications that can be specific to the IAC cases such as anesthetic complications (eg, reaction to anesthetic drugs, aspiration pneumonia), excessive blood loss, a lack of technical success (inability to access the blood supply or administer chemotherapy), or embolization/thrombosis after treatment were not encountered in these cases. Although the IAC technique requires general anesthesia and therefore associated potential risks, these did not appear to contribute to complications in this study. In addition, the procedure times were of relatively short duration.

As arterial cannulation is performed, it is important to consider the means of closure of the arterial site. Options for closure in dogs include ligation of the artery, vascular repair, manual pressure after the procedure, or vascular closure devices. Because of expense, vascular closure devices are not often utilized in clinical canine cases; additionally, these devices are generally not recommended for closure of carotid artery sites. Ligation of the artery was chosen in this study as this tends to be well-tolerated in the dog as a result of abundant collateral circulation.[25,26] Femoral artery access sites were chosen fairly distal in the groin to permit subsequent access to the same femoral artery for potential future interventions. The collateral vasculature associated with the femoral artery of dogs helps maintain blood flow and limits thrombosis in most cases; the authors have accessed a single femoral artery up to 4 times in dogs. In the one case that underwent bilateral common carotid artery ligation, after ligation neurologic dysfunction was noted. The bilateral ligation of the common carotid arteries has been demonstrated experimentally to be tolerable in dogs.[25,26] However, based on the results in this one case, the recommendation of performing IAC while utilizing the common carotid artery bilaterally needs to be cautiously undertaken in dogs.

Major complications secondary to chemotherapy administration were not noted in the IAC group. A proposed advantage of IAC over IVC is the lower potential adverse effects associated with chemotherapy.[20] Research in laboratory rabbits with bladder tumors determined that internal iliac artery infusion of carboplatin and pirarubicin was safely tolerated and resulted in significantly higher chemotherapy levels within the bladder tumor itself.[27] In addition, all tumors receiving intraarterial treatment reduced in size with 37.5% disappearing compared to those receiving intravenous treatment in which all tumors grew in size.[27] The improved efficacy of intraarterial drug delivery is thought to result from the initial increased drug concentration in the tumor after intraarterial administration. Higher local chemotherapy concentrations would translate into lower systemic chemotherapy exposures and possibly reduced systemic adverse events. Another study in laboratory dogs receiving internal iliac artery infusion of pirarubicin demonstrated tolerability and the bladder mucosa and muscle concentrations of chemotherapy were 8 times higher than that of dogs receiving IVC. In addition, the perivesical adipose tissues, pelvic lymph nodes and prostate all had significantly higher tissue levels when compared with intravenous administration.[28] The increased drug level in the regional tissues and lymph nodes might in fact be an additional advantage with this approach since multifocal vesical implant metastasis, prostatic involvement, and regional lymph node metastasis are common sites of tumor progression in dogs with lower urinary tract tumors.

The authors chose to utilize the NSAID meloxicam because of its readily available injectable formulation as well as the literature suggesting antitumor activity in laboratory tumor models with a wide range of various types of carcinomas and sarcomas.[29,30] There are no published reports of the use of meloxicam in canine TCC, to the authors' knowledge, however, the results from in-vitro as well as in-vivo mice tumor models are promising.[29,30] As other studies have confirmed the efficacy of piroxicam and deracoxib[4,16,17], it is important to consider that many NSAIDs might have antitumor properties, but there is still much to be elucidated about what NSAID (if any) could be considered the treatment-of-choice. Furthermore, the intravenous administration of NSAIDs has been shown to result in higher plasma concentrations and extravascular penetration when compared to oral administration.[31] It remains unclear if the use of different NSAIDs in the IVC cases or the use of NSAIDs administered PO versus intraarterially in this report led to the comparatively worse tumor response rates.

Ultrasonography was used to assess the initial tumor response to the evaluated therapies because of the noninvasive nature and easy accessibility to this diagnostic modality. Additionally, many clinics utilize ultrasonography to monitor tumor response to chemotherapeutics and for the presence of recurrence or further dissemination. It should be considered, however, that the evaluation of lower urinary tract neoplasia size can be highly variable when evaluated with ultrasonography and has been shown to be affected by the operator as well as the volume of the bladder.[32] Additionally, the tumors varied in size, and it is possible that it might be difficult to obtain an accurate measurement of a small tumor as compared to a large tumor. As the cases were evaluated retrospectively, images were not obtained uniformly as a specific protocol for image acquisition was not utilized and different radiologists acquired the images originally.

The RECIST criteria referenced in this study exclude the use of ultrasonography for tumor response evaluation

because of these inherent limitations; however, ultrasonography was still used in this project because of its clinical relevance for management of these tumors in dogs. Recently, the use of 3-D ultrasonography demonstrated high accuracy in determining tumor volume when compared to CT, which was considered the preferred reference method.[33] In many clinics, anesthesia is utilized to perform CT and MRI in dogs potentially preventing those imaging modalities from being used regularly in a clinical setting to monitor tumor size and response to therapy; however this might be less limiting if the patient will already be under general anesthesia for IAC administration.

There are several limitations of this study that should be discussed. The study was performed retrospectively and descriptively, and required data recording from medical records. This process is always associated with inherent inaccuracies, and the potential for incorrectly recorded data or loss of information exists. This study only evaluated the initial tumor response as the before treatment ultrasonography measurements were only compared to the first after treatment measurements. These results are short-term, and a more uniform assessment involving more time points as well as long-term and final outcome should be performed. One of the potentially more significant limitations is in regards to ultrasonographic tumor measurements. Although a single radiologist reviewed all studies and performed her own measurements on each case, the radiologist was still limited to reviewing images obtained by the initial radiologists. Additionally, not every radiologist obtained images in transverse as well as sagittal imaging planes, nor did every case have cine video loops (which could make the reviewing process more "real time"). Also, it is standard at our institutions that when a radiologist is reevaluating a patient, previously obtained ultrasound images will be reviewed in an effort to obtain images and measurements in a very similar plane, to minimize the inherent operator dependent differences in tumor assessment; this results in the radiologist's ability to perform follow-up measurements in imaging planes similar to those used in the original study. It is also noteworthy that some of the static images had measurements recorded by the attending radiologist and the measurements obtained in retrospect by the reviewing radiologist were consistent with that obtained originally.

There are a few limitations of performing this procedure specifically. As stated above, only individuals who have significant experience with interventional procedures and instrumentation should perform these IAC procedures. The NSAID administration was not standardized in the IVC group, and cases in the IAC group that received meloxicam only were compared to cases in the IVC group that received various NSAIDs; further, dogs in the IVC group received oral NSAIDs while dogs in the IAC group received intraarterial NSAIDs. The clinical consequences of this variation cannot be interpreted. Additionally, the procedure requires sacrifice of an artery if vascular ligation is elected. Although this is generally well-tolerated, this might decrease the number of times that a vessel can be accessed thus limiting the number of possible treatments. Lastly, the procedure requires anesthesia, which always poses inherent risks.

Several future studies should be considered based on the results of this initial study. Although the initial response to the combination of carboplatin and meloxicam is encouraging, other chemotherapeutics can be evaluated. Ideally, a prospective, randomized trial would be conducted that can evaluate a chemotherapy protocol that is the same for both IA and IV administration. Current work includes the evaluation of systemic drug levels after chemotherapy administered via the intraarterial and intravenous routes, and additional correlation with the development of adverse events could be made. Lastly, future studies might employ the use of other imaging diagnostics to assess the tumor response in a way that might be more reliable then ultrasonography alone; while the clinical application of this might be limited, these assessments could provide a guideline for future therapeutics.

In conclusion, this study demonstrated successful IAC administration in a cohort of dogs with lower urinary tract neoplasia. Additionally, a significantly greater reduction in tumor size (longest unidimensional measurement) was noted when comparing IAC to IVC, although the follow-up time was short and the impact on long-term outcome and survival was not determined. Further investigation is necessary to determine the potential for regular application of this technique in the treatment of canine lower urinary tract neoplasia and other solid tumors with poor response to systemically administered chemotherapy.

Footnotes

[a] PDS®, Ethicon Inc, Somerville, NJ
[b] Veni-Systems Clear Cath, Abbott Laboratories, Sligo, Ireland
[c] Weasel wire, Infiniti Medical LLC, Menlo Park, CA
[d] Introducer Sheath, Infiniti Medical LLC, Menlo Park, CA
[e] Berenstein Catheter, Infiniti Medical LLC, Menlo Park, CA
[f] Omnipaque 240 (iohexol), GE Healthcare Inc, Princeton, NJ
[g] Cobra Catheter, Infiniti Medical LLC, Menlo Park, CA
[h] Simmons Catheter, Infiniti Medical LLC, Menlo Park, CA
[i] Microwire, Infiniti Medical LLC, Menlo Park, CA
[j] Microcatheter, Infiniti Medical LLC, Menlo Park, CA
[k] Monocryl®, Ethicon Inc, Somerville, NJ

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Conflict of Interest Declaration: Dr Culp, Dr Weisse, and Dr Berent have all taught laboratories sponsored by a company that makes instrumentation that can be used to perform some of these procedures. In addition, Dr Weisse is an equity holder of this same company.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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