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INTRODUCTION
Transitional cell carcinoma is the most common malignancy affecting the urinary bladder in dogs. The disease most often affects the trigone region of the bladder, making urinary tract obstruction likely and complete surgical excision difficult at best. At the time of diagnosis, TCC in dogs is usually invasive and advanced, such that local therapies including intravesicular BCG and laser ablation that are quite successful in people are not effective in canine patients. Furthermore, the high metastatic rate (~50%) of TCC in dogs necessitates systemic therapy in order to prolong survival if local disease control can be accomplished. Various combination chemotherapy regimens have been evaluated for treatment of canine TCC (see Table 1). The most commonly utilized regimens are the mitoxantrone and piroxicam combination evaluated in a Veterinary Cooperative Oncology Group (VCOG) study or various combinations of cisplatin and nonsteroidal anti-inflammatory drugs (NSAIDs). Although a combination of cisplatin and piroxicam has provided the best objective tumor response rates to date (>71% measurable responses), drug-induced nephrotoxicity is a frequent and dose-limiting complication that precludes clinical application of this combination. Recent clinical research has focused on evaluating newer NSAIDs that are more COX-2 selective, with the intention of improving the renal safety profile of the combination of platinum agents with NSAID therapy. However, these newer combination protocols have not entirely eliminated the nephrotoxicity of cisplatin-containing regimens. This is of particular significance for dogs with urinary tract malignancy, as it frequently involves an obstructive nephropathy, which in turn, appears to substantially increase the probability of renal toxicity and dysfunction, particularly when nephrotoxic chemotherapy agents are administered. Clearly, novel strategies to prevent cisplatin and NSAID nephrotoxicity are needed in order to develop safer and more effective treatment protocols for canine TCC. This session will discuss current areas of investigation and current recommendations for clinical management of dogs with bladder cancer.

NSAIDS
Although most studies of NSAID use for treatment of canine TCC have evaluated piroxicam, there is interest in using more COX-2 selective drugs in hopes of decreasing the potential for gastrointestinal and renal side effects. Deracoxib was evaluated as a single agent in 26 client-owned dogs, using a dosage of 3 mg/kg/day. Tumor responses were assessed in 24 dogs and 17% had partial remission, 71% had stable disease, and 13% had progressive disease. Median survival time (MST) was 323 days, with those going on to receive additional therapy faring better (MST = 371 days) than those that did not (MST = 312 days). Gastrointestinal toxicity occurred in five (19%) dogs, but renal (n=1) and hepatic (n=1) toxicity were uncommon. The author and others have also investigated firocoxib in a randomized prospective trial and found a similar (17%) response rate (unpublished data). To date, piroxicam has been shown to be more likely to produce complete remissions, but overall remission rates for COX-2 selective drugs are comparable, with more favorable toxicity profiles.
GEMCITABINE
Gemcitabine is an antitumor antibiotic with promising efficacy against human urothelial tumors. Although not widely investigated in veterinary oncology to date, gemcitabine infused over less than 60 minutes once weekly at a dosage of 800 mg/m² has a favorable toxicity profile in dogs. In an effort to determine toxicity and the potential for synergistic or additive cytotoxicity against canine TCC, Marcanato, et al, conducted a prospective clinical trial enrolling 38 dogs with TCC of the urinary bladder. Gemcitabine (800 mg/m² IV q7d infused over 30 to 60 minutes) and piroxicam combination therapy provided a 27% overall response rate including two complete responders. Renal toxicity was not noted, but gastrointestinal toxicity (primarily emesis within 24 to 36 hours) occurred in 26 of 38 dogs. The MST was 230 days from time of treatment initiation. The authors concluded that this protocol may be a reasonable alternative for patients with factors that preclude the use of more nephrotoxic drug combinations such as those containing platinum drugs.

VINBLASTINE
Vinblastine has been evaluated prospectively for the treatment of histologically-confirmed TCC. At 3.0 mg/m² IV q2wks until tumor progression or unacceptable toxicoses in 28 dogs, 10 had partial remission and 14 had stable disease. The 36% response rate is comparable to that reported for mitoxantrone and piroxicam. Median survival time from first vinblastine treatment to death was 122 days (range, 28 to 476 days) and from original diagnosis to death was 299 days. Although the survival benefit was less than seen with cisplatin or mitoxantrone-based protocols, this drug offers a reasonable alternative for medical therapy of canine TCC.

Table 1: Summary of reported clinical trials of chemotherapy and NSAID administration for treatment of canine TCC of the urinary bladder

<table>
<thead>
<tr>
<th>Drugs</th>
<th># of dogs</th>
<th>Prospective or Retrospective</th>
<th>Response rate</th>
<th>MST (days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin alone</td>
<td>15</td>
<td>Retro</td>
<td>20%</td>
<td>NR</td>
<td>Increased dosage did not equate to improved response rate</td>
</tr>
<tr>
<td>Cisplatin alone</td>
<td>18</td>
<td>Pro</td>
<td>16%</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Carboplatin alone</td>
<td>14</td>
<td>Pro</td>
<td>0%</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Piroxicam alone</td>
<td>34</td>
<td>Pro</td>
<td>18%</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Carboplatin/ Piroxicam</td>
<td>31</td>
<td>Pro</td>
<td>38%</td>
<td>161</td>
<td>No nephrotoxicity noted, but GI toxicity in 74% and bone marrow toxicity in 35%</td>
</tr>
<tr>
<td>Doxorubicin/ cyclophosphamide</td>
<td>11</td>
<td>Retro</td>
<td>NR</td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone/ Piroxicam</td>
<td>49</td>
<td>Pro</td>
<td>35%</td>
<td>350</td>
<td>75% of dogs had clinical improvement, even if tumor did not have measureable remission; GI and renal toxicity in &lt;15%</td>
</tr>
<tr>
<td>Laser ablation, then Mitoxantrone/Piroxicam</td>
<td>8</td>
<td>Pro</td>
<td>100%</td>
<td>299</td>
<td>Response rate reflects the fact that tumors were laser ablated</td>
</tr>
<tr>
<td>Cisplatin/ piroxicam</td>
<td>14</td>
<td>Pro</td>
<td>71%</td>
<td>246</td>
<td>Renal toxicity in 12/14 dogs</td>
</tr>
</tbody>
</table>
**TAVOCEPT**

Tavocept (also known as BNP7787; BioNumerik, Inc, San Antonio, TX, USA), is an investigational new drug with potential to prevent or mitigate common and serious toxicities associated with chemotherapy. Tavocept has also demonstrated the ability to substantially potentiate antitumor activity of cisplatin and paclitaxel in animal studies and human clinical trials. Tavocept has been undergoing international development in human trials, including multiple Phase I, II and III clinical trials. Two randomized multicenter controlled trials of Tavocept in human patients with inoperable non-small cell lung cancer demonstrated very large increases in survival of chemotherapy-naive patients with primary adenocarcinoma, all of whom were treated with cisplatin + taxane therapy. In Japan there was a 4.6-month (vs. placebo) and in the US there was a 6.7-month (vs. no Tavocept) relative increase in overall patient survival. These are substantially larger survival increases relative to those with other agents, including bevacizumab (2 months). In both trials, there was substantial evidence that Tavocept is effective in preventing or mitigating cisplatin-induced renal toxicity. There is also strong evidence from these trials that Tavocept can prevent or mitigate chemotherapy-induced anemia and emesis. In preclinical studies including dogs, Tavocept has proven to prevent cisplatin-induced renal toxicity, emesis and anemia. The author is currently conducting a prospective clinical trial to investigate the combination of Tavocept, cisplatin, and piroxicam for treatment of canine urinary bladder TCC. Current results will be provided.

**URETHRAL STENTING**

The use of balloon-expandable metallic stents (BEMS) or self-expanding metallic stents (SEMS) has been investigated as a palliative treatment option in dogs with malignant urethral obstruction. In one report of 13 stent placements in 12 dogs (3 BEMS and 9 SEMS) all dogs were able to urinate immediately after the procedure. Three of the four females and six of eight male dogs were continent or mildly incontinent after stenting. The remaining three dogs developed complications including severe incontinence (n=2) and atonic bladder (n=1). Overall, seven of twelve dogs were considered to have an excellent outcome, with effective palliation of their urethral obstructions. This procedure is costly and requires specialized equipment, but may offer a reasonable option for select cases where urethral obstruction is life-limiting.

**ULTRASOUND-GUIDED ENDOSCOPIC DIODE LASER ABLATION**

Dogs with urinary obstruction may experience palliation of clinical signs following transurethral endoscopic laser ablation. In one report of 38 dogs treated with this technique, the median survival time was 380 days (range, 11 to 1906 days) and no difference in survival time was noted between those with or without urethral involvement. Potential complications include hematuria, stranguria, post-ablation stenosis, urethral perforation, bacterial cystitis, and spread/seeding of TCC within the lower urinary tract. Although this technique is not yet widely employed, initial results are promising.
CONCLUSIONS
In the past decade we have witnessed progress in the treatment of canine bladder and urethral cancer, from the recognition that NSAIDs have antitumor activity against TCC to more recent evaluation of combination chemotherapy and NSAID protocols. Other interventions to provide palliation such as transurethral tumor resection and urethral stenting may improve quality of life for affected dogs, as well. Radiation, immunotherapy, photodynamic therapy, and intravesicular therapy are additional treatment modalities that have not been addressed here, but may be discussed, time permitting. Remaining challenges include how to detect disease earlier and how best to limit the adverse effects associated with therapeutic intervention. Where applicable, updates regarding these challenges will be discussed.

REFERENCES