



NOTE

Internal Medicine

Use of oral paclitaxel for the treatment of bladder tumors in dogs

Hyung-Kyu CHAE^{1) #}, Ji-In YANG^{1) #}, Ju-Hyun AN¹⁾, In-Hyun LEE²⁾,
Min-Hee SON²⁾, Woo-Jin SONG^{3) *} and Hwa-Young YOUN^{1) *}

¹⁾Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Science, College of Veterinary Medicine, Seoul National University, Seoul 08826, Republic of Korea

²⁾Daehwa Pharmaceutical Company Co., Ltd., Seoul 06699, Republic of Korea

³⁾Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Jeju National University, Jeju 63243, Korea

ABSTRACT. An oral paclitaxel formulation that overcomes the hypersensitivity reaction of paclitaxel has been evaluated for safety and efficacy in humans, but not in dogs. We present the first case report on the use of oral paclitaxel in dogs. In this study, oral paclitaxel was well-tolerated in four dogs with either transitional cell carcinoma or prostate cancer; adverse effects were limited to mild neutropenia. Each of the dogs had progressive disease at the end, but clinical responses, including changes in mass size and improvement of clinical symptoms, were confirmed in some of the animals following oral paclitaxel chemotherapy. Although this study is somewhat limited by a small sample size, it suggests that oral paclitaxel may be a chemotherapeutic option for malignant tumors in dogs.

KEY WORDS: chemotherapy, cremophor EL, dog, paclitaxel, transitional cell carcinoma

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Paclitaxel, a member of the taxane family, is a microtubule-affecting cytotoxic drug that promotes microtubule polymerization and stabilization [10, 17]. By targeting tubulin, it induces abnormal mitotic spindle assembly and prevents microtubules from disassembly. As a result, paclitaxel arrests the cell cycle in the G0/G1 and G2/M phases, suppressing indiscriminate proliferation of tumor cells [21]. Paclitaxel has been used in human medicine for the treatment of recurrent or inoperable tumors such as metastatic breast, advanced ovarian, and non-small-cell lung cancers [5, 12, 15]. Paclitaxel and other taxanes have been used alone and in combination with other drugs to treat bladder tumors in humans, and its effectiveness and safety have been confirmed [2, 13]. The use of paclitaxel in the treatment of human cancers and the report of anticancer effects in various canine tumor cell lines have caused paclitaxel to be of interest for the treatment of some malignant tumors in veterinary medicine [1, 7, 8, 19].

However, the clinical use of taxanes is limited by their poor solubility in water. Therefore, vehicles such as Cremophor EL (BASF Corp., Ludwigshafen, Germany) that increase solubility are added to improve drug delivery to tumor cells; however, these vehicles cause adverse effects such as hypersensitivity reactions when administered intravenously (IV) [1, 10]. Recently, an oral paclitaxel formulation has been developed to overcome these hypersensitivity reactions, and effects similar to those of the drug's IV formulation have been reported [4]. A three-phase study of oral paclitaxel formulation in human patients with various tumors has been conducted [4, 11].

In this report, we describe the first use of oral paclitaxel for veterinary (canine) patients. We selected oral paclitaxel for the treatment of bladder tumors in our canine patients for the following three reasons: 1) compared to IV administration, oral administration is easier and confers less stress to the patient, less risk of hypersensitivity reactions, and fewer hospital visits; 2) we were able to receive oral paclitaxel for veterinary clinical application through an agreement with a pharmaceutical company; and 3) we assessed several studies from human medicine which used paclitaxel as either first and second line therapy in the treatment of refractory or recurrent bladder tumors and applied them to canine patient with bladder tumors [2, 9, 13, 18]. We aimed to evaluate the clinical validity of oral paclitaxel in dogs with bladder tumors. The study was approved by the Seoul National University Institutional Animal Care and Use Committee (SNU-180323-1).

A 13-year-old, 2.2 kg spayed female Maltese (Case 1) presented with dysuria for 1 month. Ultrasonography showed an irregular mass measuring 1.4 cm wide × 0.5 cm height at the trigone of the bladder (Fig. 1A), which extended into the proximal urethra. Urinary cytology showed a moderate degree of dysplasia of epithelial cells. Based on these results, transitional cell carcinoma (TCC) was provisionally diagnosed. We classified the stages of TCC according to TNM stage, referring to the following reference

*Correspondence to: Youn, H.-Y., hyyoun@snu.ac.kr, Song, W.-J.: ssong@jejunu.ac.kr

#These authors contributed equally to this work.

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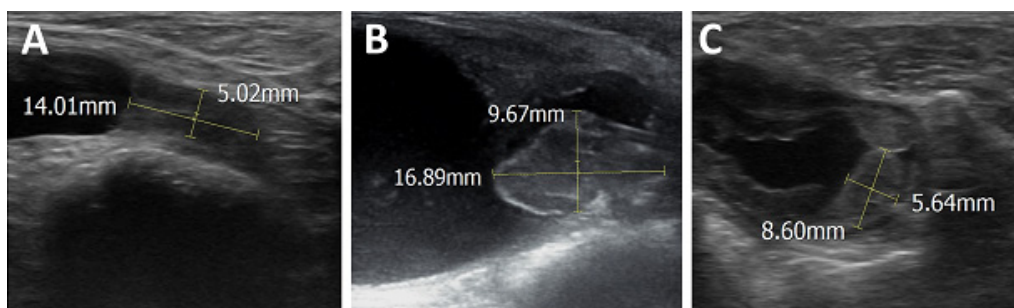


Fig. 1. Case 1 abdominal ultrasonography. (A) An irregular mass from the trigone to the proximal urethra region was observed prior to treatment. (B) An increase in mass size was observed after the first cycle of carboplatin chemotherapy. (C) A reduction in mass size was observed after the fourth cycle of oral paclitaxel.

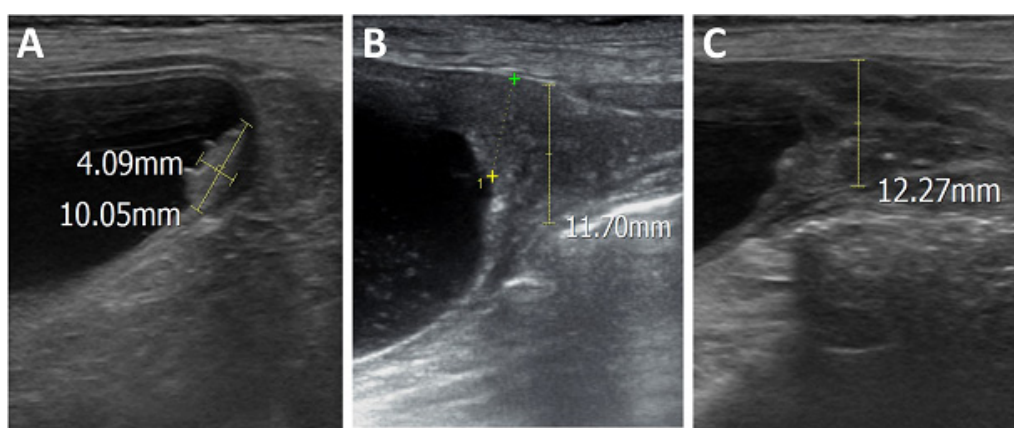


Fig. 2. Case 2 abdominal ultrasonography. (A) A mass with a broad-based attachment at the trigone was observed prior to treatment. (B) An increase in the mass size was observed after the fourth cycle of carboplatin chemotherapy. (C) No significant change in the mass height was apparent after the third cycle of oral paclitaxel.

[6]. The TNM clinical stage of the patient's bladder tumor was T3N0M0. Chemotherapy was initiated with carboplatin (Neoplatin, Boryung Pharm, Seoul, Korea; 300 mg/m² IV, every 3 weeks) and piroxicam (Crown Piroxicam, Crown Pharm, Anyang, Korea; 0.3 mg/kg PO q 24 hr). After the first cycle, ultrasonography revealed an increased tumor size of 1.6 cm wide × 0.9 cm height (Fig. 1B), with dilation of the renal pelvis. Oral paclitaxel (Liporaxel, Daehwa Pharm, Seoul, Korea) was administered as a second-line drug. The protocol involved administration on days 1, 8, and 15 every 4 weeks. The initial dose of oral paclitaxel was 5 mg/kg, which was increased by 2.5 mg/kg until the Veterinary Cooperative Oncology Group–Common Terminology Criteria for Adverse Events (VCOG-CTCAE) stage 1 toxicity was observed [16]. Neutropenia (neutrophils, $1.6 \times 10^3/\mu\text{l}$) was observed during the fourth cycle, at a dose of 12.5 mg/kg. At this time, ultrasonography revealed a reduced tumor size of 0.8 cm wide × 0.5 cm height cm², indicating a 50% decrease in size (Fig. 1C). The decrease in the size of the partial obstruction also ameliorated the dilation of the urethra and pelvis. The patient exhibited persistent weight loss associated with the tumor, with a total weight loss of 1.52 kg at the time of the last hospital visit (15 months after first visit), and was assumed to have died for reasons associated with old age and underlying disease. In this case, the overall survival time (from the date of diagnosis to the date of death) was 17 months, while the progression-free survival time (period of time without disease progression) was 11 months. After the fifth cycle of oral paclitaxel, a partial response was achieved and maintained for 6 months.

A 13-year-old, 8.2 kg spayed female Shih Tzu (Case 2) presented with dysuria for 8 months. Ultrasonography revealed an irregular mass measuring 1.0 cm wide × 0.4 cm height with a broad-based attachment at the bladder neck and mild dilation of the urethra (Fig. 2A). Cystoscopy with a bladder biopsy was performed and TCC was diagnosed. TNM clinical stage was T2N0M0. Chemotherapy was initiated with mitoxantrone (Mitron, Reyon Pharm, Seoul, Korea; 5 mg/m² IV, every 3 weeks) and piroxicam (0.3 mg/kg PO, q 24 hr). Despite two cycles of chemotherapy, ultrasonography revealed a mass extending to the urethra. As second-line chemotherapy, carboplatin (300 mg/m² IV) was administered once every 3 weeks. By the fourth cycle, dysuria had worsened, and ultrasonography revealed a mass in the proximal urethra at a height of 1.1 cm (Fig. 2B). The patient exhibited restricted activity and reduced appetite after repeated IV chemotherapy; thus, oral paclitaxel was initiated with the same protocol as in Case 1. After the third cycle, at a dose of 10 mg/kg, neutropenia (neutrophils, $2.3 \times 10^3/\mu\text{l}$) was observed. Ultrasonography revealed that the height of the mass was still 1.2 cm (Fig. 2C). However, ultrasonography at the fifth cycle revealed increased

tumor size and hypogastric lymph node enlargement. Despite chemotherapy, the patient exhibited progressive disease. Euthanasia was performed at the request of owner due to the patient's constant severe pain and poor quality of life. In this case, the patient's overall survival time was 12 months, while the progression-free survival time was 3 months.

A 12-year-old, 8 kg spayed female white terrier (Case 3) presented with dysuria and hematuria for 2 months. Urinary cytology showed hyperplasia and dysplasia of the epithelium. Ultrasonography revealed several echogenic nodules measuring 1.27 cm wide × 0.87 cm height, arising from the bladder wall, with mineralization. Contrast cystography demonstrated a mass without a filling defect. Based on the above-mentioned results, we provisionally diagnosed TCC. As imaging confirmed that the mass had not invaded the muscle layer, the TNM clinical stage was T1N0M0. Oral paclitaxel was administered immediately as induction chemotherapy with the same protocol as was used in Case 1. After the second cycle, at a dose of 7.5 mg/kg, the patient's hematuria improved, and ultrasonography revealed a stable mass. After three cycles of oral paclitaxel, surgical resection was performed, and TCC was confirmed by biopsy. This patient is still alive; to date, the patient's overall survival time is 18 months, with a progression-free survival time of 12 months. We observed an improvement in hematuria after the third cycle. No hematologic toxicity was observed with dosages of up to 7.5 mg/kg.

An 8-year-old, 8.4 kg castrated male Shih Tzu (Case 4) presented with dysuria for 2 months. Radiography revealed a mineralized prostate gland, and ultrasonography revealed a mass involving the prostate parenchyma and measuring 2.7 cm wide × 2.0 cm height with mineralized regions. Computed tomography confirmed a prostate tumor invading the adjacent bladder trigone. We initiated chemotherapy with capecitabine (Xeloda, F. Hoffmann-La Roche Ltd., Basel, Switzerland; 500 mg/m² PO, q 24 hr) and piroxicam (0.3 mg/kg PO, q 24 hr). After 3 weeks, dysuria was ameliorated; however, we observed corneal perforation consistent with a previous report of capecitabine-associated corneal toxicity [20]. Consequently, the chemotherapy regimen was changed to oral paclitaxel as used in Case 1. Neutropenia (neutrophils, $2.3 \times 10^3/\mu\text{l}$) was observed during the sixth cycle at a dose of 10 mg/kg. The oral paclitaxel dose was reduced to 7.5 mg/kg and piroxicam (0.3 mg/kg PO, q 24 hr) was prescribed. Dysuria was ameliorated after 1 week. Ultrasonography performed through the eighth cycle showed no change in tumor size. However, during the ninth cycle, the size of the tumor increased, and gastric lymph nodes showed malignant changes. Euthanasia was performed at the request of the owner for due to the patient's hematuria, anorexia, and pain response. The patient's overall survival time was 11 months, while the progression-free survival time was 9 months.

Clinical application of paclitaxel in veterinary medicine has been limited because of the lack of research on its stability and effectiveness. Although there have been studies evaluating the efficacy and toxicity of IV paclitaxel for treating canine malignant tumors [7], the stability and efficacy of the oral formulation of paclitaxel on animal patients have not been reported. Paclitaxel-induced hypersensitivity in dogs is similar to that in humans [3, 7]. In dogs, the most commonly used paclitaxel protocol involves IV administration over 3–6 hr every 3 weeks. However, in a study investigating the toxicity of paclitaxel in 25 dogs, 14 (56%) exhibited hypersensitivity reactions, despite premedication [7].

Novel formulations of paclitaxel without Cremophor EL are currently being developed, and an oral form of paclitaxel was recently approved by the Food and Drug Administration for the treatment of human gastric cancer [14]. According to Kang *et al*, the oral paclitaxel protocol for human patients involves 200 mg/m² twice daily on days 1, 8, and 15 every 4 weeks. It showed similar results in patients receiving oral paclitaxel formulations compared to patients receiving IV paclitaxel administered every 3 weeks. [4] The dose and schedule of oral paclitaxel used to treat the canine patients in this study were based on the protocol. In addition, the medication schedule used in this study was also based on the results of pharmacokinetic studies conducted on small breed beagle dogs by Daehwa Pharmaceutical Co., Ltd. (data not shown). As a result of pharmacokinetic experiment, an appropriate dose in small animals was expected to be 5–15 mg/kg. All patients received an initial dose of 5 mg/kg, which was increased by 2.5 mg/kg every week until VCOG-CTCAE stage 1 toxicity was observed.

In this case report, we found that oral paclitaxel was well-tolerated in four dogs, and adverse effects were limited to mild neutropenia. In addition, we did not observe adverse effects such as the hypersensitivity reactions that have been observed when this drug is administered intravenously. At paclitaxel doses between 10 mg/kg and 12.5 mg/kg, we observed only mild neutropenia without other adverse effects such as gastrointestinal toxicity; this neutropenia recovered immediately after the reduction of the paclitaxel dose. Thus, oral paclitaxel was found to be safe at all doses up to 12.5 mg/kg, and dose-limiting toxicity was not observed. All four dogs exhibited progressive disease, with Cases 1 and 2 being refractory to conventional chemotherapy. After oral paclitaxel chemotherapy, a clinical response was observed in all cases. In Case 1, the best response was a partial response which was maintained for 6 months. In Cases 2, 3, and 4, the best responses were stable disease, which were maintained for 3, 12, and 9 months, respectively.

The primary limitation of this study is the small sample size. Also, our study involved only small breed dogs; further research is needed to establish proper protocols such as appropriate dose units (mg/m²) for large breed dogs. In addition, additional studies will be needed on the effects of the drug on various tumor types. In conclusion, our results suggest that oral paclitaxel may be a useful alternative to IV paclitaxel for the treatment of malignant tumors in dogs. This is the first report on the safety and clinical response of oral paclitaxel in canine cancer patients and is expected to be helpful to both researchers and clinicians.

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