Case Series

jfms Journal of Feline Medicine and Surgery

Exploration of paclitaxel (Taxol) as a treatment for malignant tumors in cats: a descriptive case series

Journal of Feline Medicine and Surgery
2015, Vol. 17(2) 186–190

DOI: 10.1177/1098612X14534436
jfms.com
SAGE

Jennifer Kim[1], Mary Doerr[2] and Barbara E Kitchell[3]

Abstract

Paclitaxel, an effective chemotherapeutic agent in human oncology, has received little evaluation in feline patients. The diluent used to solubilize paclitaxel, polyoxyethylated castor oil (Cremophor EL), causes anaphylactoid reactions in human and dogs, which limits enthusiasm for use of this agent in veterinary oncology. Nine feline patients with measurable malignant tumors were treated with paclitaxel at a dosage of 80 mg/m^2 intravenously every 21 days for up to two doses. Adverse effects, including evidence of toxicity and anaphylactoid reactions, were assessed. Tumor response, progression and patient time to progression (TTP) were also recorded. Adverse effects included grade III and IV thrombocytopenia, grade III gastrointestinal signs (vomiting and constipation) and hypersensitivity reactions, seen in a total of five patients. Anaphylactoid reactions resolved with appropriate management. Stable disease and partial response were observed in 56% of feline patients. Median TTP was 28 days (range 15–45 days). Intravenous paclitaxel is a safe treatment option for feline malignant tumor patients. Future investigation is warranted to explore the effectiveness and appropriate application of this agent for specific tumor types.

Accepted: 14 April 2014

Paclitaxel (Taxol; Bristol-Myers Squibb) is a taxane chemotherapy agent with a broad spectrum of activity against many tumor types in humans. The primary mechanism of action is to bind to tubulin, impairing the microtubule network that is requisite for completion of mitosis and interphase.[1] This drug was first discovered as a part of a National Cancer Institute program that screened natural products for antitumor activity.[2] As paclitaxel is water insoluble, it is suspended in polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol 50% for intravenous (IV) administration. Unfortunately, in dogs and humans, the Cremophor EL causes one of the most profound toxicities associated with paclitaxel use: acute anaphylactoid hypersensitivity reactions.[3]

As paclitaxel is an important drug in human oncology, we felt there was compelling rationale to explore its use as a therapeutic agent in feline oncology patients. Injection site sarcoma cell lines established from feline tumors have been shown to be sensitive to paclitaxel in vitro.[4] Docetaxel, a closely related taxane compound, was safely administered orally to cats in a phase I trial, with gastrointestinal signs being the dose-limiting toxicity. No acute hypersensitivity reactions were seen.[5] Docetaxel was given intravenously in a phase I trial, where the maximum tolerated dosage was found to be 2.25 mg/m^2 body surface area. Observed adverse side effects included fever, neutropenia and vomiting.[6] Another study assessed IV docetaxel as a treatment for metastatic mammary carcinoma in cats, which demonstrated a response rate of 84.6%.[7] Both paclitaxel and docetaxel have been tolerated by canine cancer patients, with hematopoietic (neutropenia) and gastrointestinal reactions being the dose-limiting adverse effects, respectively.[8,9]

To our knowledge, this study reports the first paclitaxel treatment case series in cats. This study reports the toxicities associated with paclitaxel administration for the treatment of advanced feline neoplasms. The dose of

[1]NorthStar VETS, Robbinsville, NJ, USA
[2]Michigan State University, East Lansing, MI, USA
[3]VCA Veterinary Care Animal Hospital and Referral Center, Albuquerque, NM, USA

Corresponding author:
Jennifer Kim DVM, NorthStar VETS, 315 Robbinsville-Allentown Road, Robbinsville, NJ 08691, USA
Email: jkim@northstarvets.com

paclitaxel used in this case series was an empirically derived dose of 80 mg/m^2, which closely approximates the published investigational dose of 5 mg/kg.[10]

Materials and methods

Patient selection

Cats presented to Michigan State University's Veterinary Cancer Care Clinic for treatment of advanced, measureable neoplasms were eligible for inclusion. Owner consent for treatment was obtained. Patients that had received previous treatments, whether surgical, medical or radiation therapy, or any combination of these, were not excluded from study participation. Exclusion criteria included life-limiting comorbid conditions resulting in limited life expectancy of <4 weeks, hepatobiliary disease resulting in hyperbilirubinemia >1.5 mg/dl and previous anaphylactic events. Patients were staged by a complete blood count (CBC), biochemistry profile, urinalysis, thoracic radiographs and, in most cases, abdominal ultrasound examination. Each patient's signalment, tumor type, location of disease, date of diagnosis and previous therapy, including other chemotherapy, surgery and/or radiation treatment, were recorded. Patients were evaluated weekly during the protocol.

Treatment protocol

Paclitaxel was administered intravenously at a dose of 80 mg/m^2 in 30 ml of 0.9% NaCl over 45 mins. Patients received an oral premedication regimen, as used in human paclitaxel patients. This pretreatment protocol was carried out for 7 days before planned paclitaxel treatment, and included prednisolone (1 mg/kg orally every 24 h), famotidine (0.5 mg/kg orally every 24 h) and diphenhydramine (2 mg/kg orally every 12 h). Thirty mins before paclitaxel administration, patients received diphenhydramine at a dose of 4 mg/kg intramuscularly, famotidine at a dose of 1 mg/kg intravenously and dexamethasone sodium phosphate at a dose of 2 mg/kg intravenously. The paclitaxel was diluted to 30 ml total volume in normal saline. The infusion was started at 15 ml/h and was increased to 30 ml/h if no evidence of anaphylactoid reaction was observed after the initial 30 mins of infusion. If signs of acute hypersensitivity were noted, the infusion was stopped and additional dexamethasone and diphenhydramine were administered at the same dose as described. Reductions in paclitaxel dose and treatment delays were instituted at the clinician's discretion based on observed toxicities. When dose reduction was deemed necessary, the dose was decreased by 25%.

Toxicity

Cats were observed for anaphylactoid reaction continuously during the paclitaxel infusion. Heart rate was recorded every 15 mins, and the patient was kept under constant visual observation during the infusion period. If any reaction was suspected, rectal temperature and respiratory rate and effort were recorded. Toxicity resultant from the infusion was assessed by physical examination, and owner assessment via a questionnaire completed at each visit. CBC profiles were performed 7 days after paclitaxel therapy. Serum biochemistry profiles were repeated in each patient before subsequent doses of treatment on a planned 21 day basis. Gastrointestinal and hematologic toxicities were graded according to a modified National Cancer Institute Common Toxicity Criteria scheme.[11]

Response

The objective of this study was to evaluate toxicity; however, measurement of macroscopic tumors was also performed, and any responses observed were documented. Internal tumors were evaluated with three-view thoracic radiographs or abdominal ultrasound every 3–8 weeks, and external tumors were measured with calipers at every visit. All patients had measurable disease at the time of paclitaxel treatment. Response to treatment was categorized as follows: complete response (CR), 100% disappearance of all macroscopic measurable disease plus no development of new lesions; partial response (PR), greater than 50% reduction in volume of measurable disease and no new lesions; stable disease (SD), less than 50% reduction in the volume of measurable disease or less than 25% increase in the volume of measurable disease plus no development of new lesions. Progressive disease was indicated when measurable lesions grew by greater than 25% in size and/or new lesions were detected. Time to progression (TTP) was defined as the time from maximal tumor response with CR or PR, or beginning of chemotherapy for patients with SD, until time of measurable tumor progression. Overall survival is defined as the time from initial diagnosis until death or euthanasia due to disease progression.

Results

Patient characteristics

From July 2004 to October 2008, nine cats with cancer were treated with paclitaxel. The breeds represented were domestic shorthair (n = 6), Siamese (n = 2) and domestic longhair (n = 1). All patients were neutered, with seven female and two male cats included. The median age was 12 years (range 7–16 years). Median weight at time of treatment was 3.9 kg (range 3.1–5.9 kg).

Tumor characteristics

In this patient cohort, six cats had mammary adenocarcinomas, one had osteosarcoma, one had liver carcinoma and one with apocrine gland adenocarcinoma. Eight of these were confirmed by histopathology and the liver carcinoma was a presumptive diagnosis based

on abdominal ultrasound and cytology of ascites. All but the cat with presumed liver carcinoma had surgery as their primary treatment. The patient with osteosarcoma had also received radiation therapy before paclitaxel treatment. At the time of first treatment, all nine patients had measurable disease, and eight of these patients had gross metastatic disease to lung or lymph node.

Treatment

During the course of the study, 14 doses of paclitaxel were administered in total, with five cats each receiving two doses and four cats each receiving one dose. All cats received their initial dose as planned, while two cats had subsequent dose reductions (25%) owing to toxicity.

Hematologic toxicity

Thrombocytopenia developed in two patients (22%), one of which had grade III and one of which had grade IV thrombocytopenia.

Gastrointestinal toxicity

Two cats (22%) experienced gastrointestinal toxicity that included grade III vomiting in two cats and reported constipation in one cat (11%). One cat had both vomiting and constipation.

Hypersensitivity

Signs of anaphylaxis during paclitaxel administration were seen in two cats with their first infusions. These signs included fever, tachycardia and tachypnea. In both cases, administration of paclitaxel was discontinued; additional diphenhydramine and dexamethasone were administered. The cats were closely monitored until resolution of signs. Signs of anaphylaxis resolved in one cat, and the paclitaxel infusion was subsequently restarted at a slower rate of infusion. Infusion was discontinued in the other cat and the signs resolved.

Response

The overall response rate for this limited cohort of patients was 56% (5/9). Four patients (44%) achieved SD and one patient (11%) had a PR. Of the cats with response, 4/5 (80%) had mammary carcinoma, including the patient with a PR. The remaining patient that experienced SD had osteosarcoma with pulmonary metastasis. The patient experiencing PR was being treated for metastatic and locally recurrent mammary adenocarcinoma. This cat had reduction in volume of thoracic metastatic disease, as well as regression of recurrent disease in the lymph node. Median TTP was 27 days (range 15–45 days). For feline patients that had a response, median TTP was 28 days (range 15–45 days), and median TTP for non-responders was 24 days (range 15–42 days) (Table 1).

Discussion

In this case series, IV administration of paclitaxel appeared to be well tolerated by feline patients. Two patients experienced hypersensitivity reactions. Upon careful questioning of the owners of these cats, the anaphylactoid responses may have been attributable to suboptimal premedication because of lack of owner compliance. Two patients developed thrombocytopenia; both of these cats had also experienced neutropenia when they received carboplatin before participation in this study. This would suggest that cats are more likely to develop bone marrow toxicity affecting the platelets, rather than neutropenia that predominated in paclitaxel-treated dogs.[8,9] Two cats experienced vomiting, and one cat had constipation. Interestingly, no neutropenia was observed in these feline patients, which differs from the toxicity noted in canine patients treated with paclitaxel. The dosage used in this sample of feline patients was lower than that used in canine patients, where the maximum tolerated dose was found to be 132 mg/m^2.[8] Two cats required dose reductions for their second paclitaxel treatment. One of these dose reductions was a result of anaphylactoid reaction, as well as constipation and vomiting. The second cat treated with a 25% dose reduction suffered grade IV thrombocytopenia after the first dose of paclitaxel. The cat with significant vomiting had the presumptive diagnosis of hepatocellular carcinoma. Thus, the vomition in this case could have been due to the liver malignancy rather than an adverse drug reaction.

In this study, cats received a median of two doses of paclitaxel. All cats included in the study had advanced disease at the time of inclusion. One cat treated for mammary adenocarcinoma received paclitaxel as the first therapy and failed to respond. All other patients received paclitaxel treatment as rescue therapy. One cat had been treated by four previous chemotherapy protocols, three cats had three treatments and four cats had two protocols for a median of two previous chemotherapy treatments prior to initiation of paclitaxel therapy. These other chemotherapy protocols include gemcitabine with carboplatin, doxorubicin with cyclophosphamide, and lomustine, vinorelbine, doxorubicin, carboplatin, mitoxantrone and ifosfamide, each administered as single agents. The patient that achieved a PR had received mitoxantrone, carboplatin and gemcitabine with carboplatin before receiving paclitaxel.

Overall response rate was 56% (5/9). Of the four cats that achieved disease stabilization, three had mammary adenocarcinoma and one had osteosarcoma. While paclitaxel is commonly used to treat advanced breast cancer in women, paclitaxel has not been associated with response in human osteosarcoma.[12,13] However, two dogs with metastatic osteosarcoma were reported to have measurable responses.[8] In our study, one patient

Table 1 Clinical data of nine cats receiving paclitaxel

Patient	Diagnosis	Response	No. of previous protocols	No. of paclitaxel treatments	TTP (days)*	OS (days)†
1	Apocrine gland ACA	PD‡	4	2	42	288
2	Mammary ACA	PD‡	0	1	15	197
3	Mammary ACA	SD§	2	1	15	252
4	Osteosarcoma	SD§	3	1	25	432
5	Mammary ACA	SD§	2	2	107	236
6	Mammary ACA	PR¶	3	2	28	1060
7	Mammary ACA	SD§	2	2	45	407
8	Hepatic CA	PD‡	2	2	27	352
9	Mammary ACA	PD‡	3	1	22	202

TTP = time to progression; OS = overall survival; ACA = adenocarcinoma; PD = progressive disease; SD = stable disease; PR = partial response; CA = carcinoma
*Time from maximal tumor response for patients with complete response or PR, or from beginning of paclitaxel treatment for patients with SD, until the time of measurable tumor progression
†Time from initial diagnosis to death or euthanasia owing to disease progression
‡Growth of lesions by >25%, or development of new lesions
§<50% reduction in the volume of measurable disease or <25% increase in the volume of measurable disease plus no new lesions
¶>50% reduction in volume of measurable disease with no new lesions

with osteosarcoma had SD. Thus, using paclitaxel for osteosarcoma feline patients may warrant further study. Disease stabilization was determined in these cases by observation of regression of initial tumor volume by <50% with no new lesions observed. Thus, the sole fact that tumor burden was diminished was the criterion for declaration of stabilization, as this indicates that paclitaxel had activity against the tumor cells. Unfortunately, this regression in observed tumor volume was of brief duration for most of these cats, as would be expected in refractory, end-stage neoplasms. Only two patients (cats 5 and 7; see Table 1) would qualify under more stringent criteria of disease stabilization for a duration of 6 weeks.[14]

Conclusions

While a dose escalation protocol was not performed in this series of cases, the grade III and IV toxicities observed here suggest that the 80 mg/m^2 dosage used approximates the maximum tolerated dose. The noted toxicities were manageable and no cats died as a result of toxicity. Dosage optimization studies could be carried out with the current dose as a starting point. It is important to note that the majority of the cats in this study were relapsed, progressive and heavily pretreated. Future directions for exploration of paclitaxel in feline patients include an appropriately powered phase II efficacy study for cats with advanced mammary carcinomas. Additionally, novel formulations of paclitaxel that do not employ Cremaphor EL as a solubilizing agent, such as the micellated form currently under investigation in canine patients, could alleviate the hypersensitivity reactions noted here.[15–18] Paclitaxel is considered a very useful chemotherapeutic agent in human oncology, and it is encouraging to note the modest response rate seen here, as well as the toxicity profile of this agent as a basis for further exploration.

Acknowledgements We would like to acknowledge Erin Mayo for her editorial assistance on this manuscript, as well as the contributions of the oncology residents and technicians at Michigan State University's Animal Cancer Care Clinic for clinical management of these cases.

Conflict of interest The authors do not have any potential conflicts of interest to declare.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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