Article

A retrospective study of proteinuria in dogs receiving toceranib phosphate

Sindy L. Piscoya, Kelly R. Hume, Cheryl E. Balkman

Abstract — The incidence of proteinuria in humans receiving tyrosine kinase inhibitors has been well-documented. Reports of proteinuria with this class of drugs are limited in veterinary medicine. This retrospective study describes the incidence, severity, and progression of proteinuria in 55 dogs treated with toceranib phosphate, with or without concurrent glucocorticoid or NSAID (non-steroidal anti-inflammatory drug). Six dogs were proteinuric at baseline. Twelve of the 49 dogs that were not proteinuric at baseline developed proteinuria while receiving toceranib phosphate. Median urine protein:creatinine (UPC) ratio when proteinuria developed was 0.75 (range: 0.6 to 4.9). There was no association with intermittent glucocorticoid or NSAID use and development of proteinuria ($P = 0.5$ and $P = 0.7$, respectively). Overall duration of toceranib phosphate treatment ranged from 70 to 802 days in proteinuric dogs and 28 to 1285 days in non-proteinuric dogs. Our results indicate a subset of dogs receiving toceranib phosphate may develop proteinuria; careful monitoring with serial UPCs is recommended.

Résumé — Étude rétrospective de la protéinurie chez des chiens recevant du phosphate de tocéranibe. L'incidence de protéinurie chez les humains recevant des inhibiteurs de la tyrosine kinase a été bien documentée. Les rapports de protéinurie avec cette classe de médicaments sont limités en médecine vétérinaire. Cette étude rétrospective décrit l'incidence, la gravité et la progression de la protéinurie chez 55 chiens traités à l'aide de phosphate de tocéranibe, avec ou sans des glucocorticoïdes ou des AINS (anti-inflammatoires non stéroïdiens) concomitants. Six chiens étaient protéinuriques au point de référence. Douze des 49 chiens qui n'étaient pas protéinuriques au point de référence ont développé la protéinurie pendant qu'ils recevaient du phosphate de tocéranibe. Le ratio médian de protéine-créatinine au moment du développement de la protéinurie était de 0,75 (fourchette : de 0,6 à 4,9). Il n'y avait aucune association avec l'utilisation intermittente de glucocorticoïdes ou d'AINS et le développement de la protéinurie ($P = 0,5$ et $P = 0,7$, respectivement). La durée totale du traitement au phosphate de tocéranibe s'échelonnait de 70 à 802 jours chez les chiens protéinuriques et de 28 à 1285 jours chez les chiens non protéinuriques. Nos résultats indiquent qu'un sous-groupe de chiens recevant du phosphate de tocéranibe peut développer la protéinurie et une surveillance attentive à l'aide d'une série de ratios urinaires protéine-créatinine est recommandée.

(Traduit par Isabelle Vallières)

Can Vet J 2018;59:611–616

Introduction

Over the last decade, targeting of tyrosine kinases, primarily receptor tyrosine kinases, has been of particular interest in human medicine due to the efficacy of the treatment in management of certain malignant hematologic disorders and solid tumors (1–3). While tyrosine kinase inhibitors (TKIs) are generally well-tolerated in humans, observed side effects have included cytopenias, fluid retention, gastrointestinal toxicity (i.e., nausea, vomiting, diarrhea), skin toxicity, cardiac toxicity, elevated liver enzymes, hypothyroidism, hypertension, and proteinuria (4–6). In veterinary medicine, TKIs are currently being used as targeted therapy for the treatment of various canine and feline malignancies (7–19). Perhaps the most widely used TKI in companion animals is toceranib phosphate, an orally administered receptor TKI with both direct anti-tumor and anti-angiogenic activity that inhibits members of the split kinase family including Kit, vascular endothelial growth factor receptor (VEGFR), and PDGFR (platelet-derived growth factor receptor) (20). Toceranib phosphate has been approved for use in dogs in both the US and Canada in recurrent, non-resectable Patnaik grade II or III mast cell tumors (MCTs) (8); however, it has also shown some efficacy in the treatment of many other spontaneous canine malignancies including carcinomas and sarcomas (10). The most common adverse events associated with toceranib phosphate in dogs include diarrhea, anorexia, weight loss, lethargy, and vomiting. Less common side effects include gastrointestinal bleeding, mild neutropenia, localized muscle cramping, dermatitis, increased liver enzymes, increased creatinine values, and hypertension (8,13,21). Limited information exists on the incidence of proteinuria in dogs receiving TKIs.

Cornell University College of Veterinary Medicine — Clinical Sciences, VMC Box 31, Ithaca, New York 14853-6401, USA.

Address all correspondence to Dr. Kelly Hume; e-mail: krh73@cornell.edu

The TKI masitinib has been shown to induce a protein-losing nephropathy in a small number of treated dogs, the cause of which is not clear (7,22–24). Documented reports of proteinuria in dogs receiving toceranib phosphate are scarce, aside from a short-term study aimed at investigating hypertension (21). However, it is not clear that dogs are routinely screened for this potential complication.

The pathogenesis of proteinuria following the use of TKIs has not been fully elucidated, although multiple mechanisms have been implicated, of which VEGF (vascular endothelial growth factor) plays an important role. VEGF signaling is important for the development and maintenance of the glomerular filtration barrier, which prevents renal loss of large molecules and proteins (6,25). Inhibition of VEGF can result in decreased capillary fenestrations, endotheliosis, detachment of endothelial cells, and hypertrophy that ultimately results in proteinuria (26,27). Another mechanism proposed to partially contribute to the development of proteinuria has been the development of hypertension, which may be due to inhibition of VEGF and subsequent decreased nitric oxide production or rarefaction of microvascular beds (6). Masitinib, which has been associated with protein-losing nephropathy in dogs, does not directly inhibit VEGFR (28). However, suppression of VEGF has been documented with TKIs that do not target VEGFR (29). Therefore mechanisms of proteinuria related to VEGF loss may also potentially apply to TKIs that do not target VEGFR.

Given that the incidence and severity of proteinuria in dogs receiving toceranib phosphate is not fully characterized, it is difficult to develop appropriate guidelines for screening and management of the condition. The purpose of this study was to describe the incidence and progression of proteinuria in tumor-bearing dogs receiving toceranib phosphate for a minimum of 3 wk.

Materials and methods

Medical records of dogs with any type of malignancy treated with toceranib phosphate at the Cornell University Hospital for Animals between September 2009 and October 2014 were retrospectively reviewed. Records meeting inclusion criteria were selected for further review. Inclusion criteria consisted of i) dogs with any type of malignancy treated with toceranib phosphate for a minimum of 3 wk, ii) baseline urinalysis (UA), with urine protein:creatinine ratio (UPC) results available if protein was detected in the absence of an active sediment, and iii) serial UA results available at every recheck with UPC if indicated. Toceranib phosphate (Palladia; Zoetis, Parsippany, New Jersey, USA) was administered PO on a Monday-Wednesday-Friday schedule in all dogs. All dogs receiving toceranib phosphate were monitored similarly. This included complete blood (cell) count (CBC), serum biochemistry panel, UA, and UPC (if indicated) every 2 wk for the first month and then monthly thereafter. Dogs that developed proteinuria had UPCs rechecked 1 to 2 wk after time of onset and monthly thereafter.

Age, sex, neuter status, breed, body weight, cancer diagnosis, pre-existing medical problems, concurrent administration of a nonsteroidal anti-inflammatory drug (NSAID), glucocorticoid, or omega-3 fatty acid supplement, toceranib phosphate dosage, results of UA and UPC (if performed), time to proteinuria, grade of proteinuria, duration of proteinuria, treatment for proteinuria, and duration of toceranib phosphate administration were recorded for all dogs. Proteinuria was classified based on Veterinary Cooperative Oncology Group — Common Terminology Criteria for Adverse Events (VCOG-CTCAE), in which grade 1 proteinuria was defined as having a UPC > 0.5 but < 1.0, grade 2 proteinuria as having a UPC ≥ 1.0 but transient (< 14 d in duration) and grade 3 proteinuria as having a UPC ≥ 1.0 and prolonged (≥ 14 d duration) (30). Time to proteinuria was calculated in days from start of toceranib phosphate to the date of the UPC documenting proteinuria. Duration of proteinuria was defined as the date of first abnormal UPC (i.e., grade 1 or higher) until documentation of a normal UPC, death, or loss to follow-up. Duration of toceranib phosphate treatment was calculated in days from the first dose of toceranib phosphate to the last dose of toceranib phosphate. Additional data obtained and recorded included prior adjunctive radiation therapy (definitive or palliative), previous chemotherapy, and extent of neoplastic lesion (macroscopic or microscopic). Referring veterinarians were contacted if needed for further information regarding follow-up UA, UPC, and clinical outcome.

Dogs that were not proteinuric at baseline were subdivided into 2 groups. Group 1 was comprised of dogs that received toceranib phosphate without concurrent glucocorticoid whereas Group 2 was comprised of dogs that received toceranib phosphate with concurrent glucocorticoid. In dogs that were not proteinuric at baseline, logistic regression was used to determine if glucocorticoid use, NSAID use, toceranib phosphate dosage, or duration of toceranib phosphate treatment was associated with the development of proteinuria. Statistical significance was set as $P \leq 0.05$. Analyses were performed using JMP statistical software. Dogs that were proteinuric at baseline were not included in statistical analysis and were described separately.

Results

Seventy records of dogs receiving toceranib phosphate were identified; 15 dogs were excluded from full analysis due to lack of follow-up beyond 2 wk of toceranib phosphate treatment or voluntary discontinuation of treatment. Nine of these 15 dogs did have follow-up information available 2 wk after treatment initiation and none were proteinuric. Fifty-five dogs met our inclusion criteria. Twenty-nine dogs were male (28 were castrated) and 26 were female (24 were spayed). Purebred dogs ($n = 46$) were represented by 20 breeds of which the 3 most common were: golden retriever ($n = 10$), Labrador retriever ($n = 9$), and boxer ($n = 5$). Mixed breed dogs represented 9% of the dog population in this study. Median body weight was 33.3 kg (range: 7.3 to 72.1 kg), and median age was 7 y (range: 3 to 13 y). At baseline evaluation, 45 dogs had macroscopic disease and 10 had microscopic disease. Primary tumors included mast cell tumors ($n = 29$), carcinomas of multiple types ($n = 11$), soft tissue sarcomas ($n = 9$), non-soft tissue sarcoma of multiple subtypes ($n = 5$), and 1 dog with an oral collision tumor. Ten dogs received single agent systemic chemotherapy, including mitoxantrone, vinblastine, doxorubicin, or carboplatin, before

Table 1. Characteristics of dogs receiving toceranib phosphate with or without concurrent glucocorticoid.

	Group 1: Toceranib ± NSAID (n = 25[a])	Group 2: Toceranib + glucocorticoid (n = 24)
Median (range) toceranib phosphate dosage (mg/kg BW)	2.6 (2.3 to 2.7)	2.6 (2.3 to 2.7)
Number that became proteinuric	5	7
Number with grade 1 proteinuria	2	5
Number with grade 2 proteinuria	1	0
Number with grade 3 proteinuria	2	2
Median (range) time to proteinuria (days) in affected dogs	47 (19 to 626)	69 (15 to 212)
Median (range) UPC at time proteinuria was detected	0.7 (0.6 to 4.9)	0.8 (0.6 to 1.1)
Median (range) USG at time proteinuria was detected	1.026 (1.017 to 1.033)	1.028 (1.014 to 1.044)
Median (range) creatinine (μmol/L) at time proteinuria was detected	80 (53 to 124)	97 (44 to 124)
Median (range) overall treatment duration (days) all dogs	149 (43 to 1285)	88.5 (28 to 760)

[a] Fourteen of 25 dogs also received an NSAID intermittently. BW — body weight; UPC — urine protein:creatinine ratio; USG — urine specific gravity; grade 1 proteinuria: UPC > 0.5 but < 1.0; grade 2 proteinuria: UPC ≥ 1.0 but transient (< 14 d duration); grade 3 proteinuria: UPC ≥ 1.0 and prolonged (≥ 14 d duration).

receiving toceranib phosphate. No dogs received additional chemotherapy concurrently with toceranib phosphate. Sixteen dogs previously received adjunctive external beam radiation therapy (total dose: 14 to 48 Gy) before toceranib phosphate; no dog had bladder or kidney irradiated. Six dogs were proteinuric at baseline.

Twenty-five dogs that did not have pre-existing proteinuria received toceranib phosphate without concurrent glucocorticoid (Group 1). None of these dogs received an omega-3 fatty acid supplement while receiving toceranib phosphate. Descriptive results for these dogs are presented in Table 1. Five of these dogs developed proteinuria while receiving toceranib phosphate. At the time proteinuria was detected, creatinine was within the reference interval and urine specific gravity (SG) was ≥ 1.017 in all 5 dogs; blood urea nitrogen (BUN) was increased in 1 dog (17 mmol/L) that had a urine SG of 1.031. No pre-existing medical conditions were identified in any of these dogs that could have predisposed them to proteinuria, aside from the primary cancer diagnosis. No significant clinicopathological abnormalities were identified at baseline. Fourteen of these dogs received an NSAID concurrently with toceranib phosphate. Prescribed NSAIDs included carprofen (n = 12) and piroxicam (n = 2); when prescribed, these drugs were administered at standard dosages on a Tuesday-Thursday-Saturday-Sunday (TuThSaSu) schedule. In 2 dogs that developed grade 1 proteinuria (at 28 and 47 d), a 2-week drug holiday was instituted. Their UPCs improved but did not normalize; toceranib phosphate was reinstituted with a 10% dose reduction. The UPCs were evaluated every 2 wk for the next month and monthly thereafter. The UPCs remained stable until resolution 27 and 132 d later. Three additional dogs became proteinuric and remained proteinuric. The dog that had an increased BUN at the time proteinuria was detected was initially managed with enalapril (Teva Pharmaceuticals, North Wales, Pennsylvania, USA), 0.5 mg/kg body weight (BW), PO, q24h; further follow-up was performed by the primary care veterinarian. One month after proteinuria diagnosis, both BUN (21 mmol/L) and creatinine (158 μmol/L) were elevated and UPC had increased from 4.9 to 6.3 (urine SG not available). Subsequently, a 20% dose reduction was prescribed; however, the dog's owners elected to discontinue toceranib phosphate. This dog died at home 1 mo later, 62 d after the initial proteinuria diagnosis. No necropsy was performed; however, cause of death was attributed to progression of pulmonary anaplastic sarcoma as the owner reported an onset of labored breathing before death. Another proteinuric dog was managed with a 25% dose reduction and continued to receive toceranib phosphate with stable UPC values (fluctuating from 0.6 to 1.0) until it was lost to follow-up 262 d after proteinuria was diagnosed. At the time of last follow-up, BUN and creatinine were within reference intervals and urine SG was 1.020. The last of the proteinuric dogs initially had a grade 1 proteinuria develop after 626 d of toceranib phosphate treatment. Four months later, the proteinuria progressed to grade 2. This dog continued to receive toceranib phosphate for an additional 2 mo at which time the drug was discontinued due to possible progressive disease. At the time of discontinuation, BUN and creatinine were within reference intervals and urine SG was 1.017. Four of the five dogs in Group 1 that became proteinuric were receiving an NSAID. Median time to proteinuria in these 4 dogs was 37.5 d (range: 19 to 626 d) and median toceranib phosphate treatment duration was 291 d (range: 149 to 802 d).

Twenty-four dogs that did not have pre-existing proteinuria received toceranib phosphate and prednisone or prednisolone (Group 2). Median prednisone/prednisolone dosage was 0.5 mg/kg BW (range: 0.5 to 1.0 mg/kg BW) given PO on a TuThSaSu schedule. None of these dogs received an omega-3 fatty acid supplement while receiving toceranib phosphate. Descriptive results for these dogs are also presented in Table 1. Seven of these dogs developed proteinuria while receiving toceranib phosphate. At the time proteinuria was detected, BUN and creatinine were within the reference intervals and urine SG was ≥ 1.014 in all 7 dogs. Similar to Group 1, other than cancer, none of these dogs had pre-existing medical problems that would predispose them to proteinuria. No significant clinicopathological abnormalities were identified at baseline. In 4 dogs that became proteinuric (grade 1, n = 3; grade 3, n = 1), a 2-week drug holiday was instituted. The UPCs improved but did not normalize and toceranib phosphate was reinstituted with a 10% to 14% dose reduction. The UPCs were analyzed every 2 wk for the next 4 wk and then monthly thereafter. No further spikes in UPCs were observed and proteinuria eventually resolved in these 4 dogs. Median time to resolution of proteinuria was 83 d (range: 53 to 212 d). The remaining 3 dogs that

became proteinuric did not have documented resolution of their proteinuria. Toceranib phosphate was discontinued by the owners of 2 dogs due to financial concerns. One of these dogs was lost to follow-up soon after proteinuria was diagnosed; the other dog received toceranib phosphate for an additional 36 d after proteinuria was diagnosed before being lost to follow-up with a stable UPC. Toceranib phosphate was discontinued in the third dog due to tumor progression 70 d after proteinuria developed; proteinuria was stable at this time, and the owners elected not to return for further evaluation. These 3 dogs did not have increased BUN or creatinine at the time of last evaluation, and urine SG ranged from 1.022 to 1.047.

In summary, 12 of 49 dogs (24%) without pre-existing proteinuria developed proteinuria while receiving toceranib phosphate. Seven dogs (14%) developed grade 1 proteinuria, 1 dog (2%) developed grade 2 proteinuria, and 4 dogs (8%) developed grade 3 proteinuria. At the time of proteinuria diagnosis, median UPC was 0.75 (range: 0.6 to 4.9), median creatinine was 88.4 μmol/L (range: 44 to 124 μmol/L), and median urine SG was 1.027 (range: 1.014 to 1.044). Resolution of proteinuria was documented in 6 dogs (50%) that continued to receive a reduced dose of toceranib phosphate after temporary drug discontinuation. Five dogs (42%) had relatively stable proteinuria until progressive disease developed, toceranib phosphate was discontinued for other reasons, or the dog was lost to follow-up. One dog (8%) with pulmonary anaplastic sarcoma did have worsening proteinuria and onset of azotemia; however, death in this dog was attributed to cancer progression based on reported clinical signs.

Neither glucocorticoid use ($P = 0.5$), NSAID use ($P = 0.7$), nor toceranib phosphate dosage ($P = 0.2$) was associated with development of proteinuria. We did detect an association between duration of toceranib phosphate treatment and development of proteinuria ($P = 0.005$). For all 49 dogs, median duration of toceranib phosphate treatment was 118 d (range: 28 to 1285 d). For dogs that became proteinuric, median duration of toceranib phosphate treatment was 257 d (range: 70 to 802 d), compared to 112 d (range: 28 to 1285 d) for dogs that did not become proteinuric. However, the median time to proteinuria in affected dogs was 51.5 d (range: 15 to 626 d), with 4 dogs developing proteinuria within 30 d, 4 dogs between 30 and 90 d, and 4 dogs after 90 d. Only 1 dog developed proteinuria after more than 130 d of toceranib phosphate treatment.

In the 6 dogs found to be proteinuric at baseline, median UPC was 1.75 (range: 0.7 to 3.9), median creatinine was 71 μmol/L (range: 62 to 97 μmol/L), and median USG was 1.027 (range: 1.016 to 1.049). The only other clinicopathologic variable of interest at baseline in these 6 dogs was a grade 1 (30) BUN elevation in 1 dog. Creatinine was within the reference interval and urine SG was 1.016 in this dog (UPC was 2.3). As in Groups 1 and 2, none of these dogs had pre-existing medical problems other than cancer that would predispose them to proteinuria. The median dosage of toceranib phosphate for all 6 dogs was 2.6 mg/kg BW (range: 2.3 to 2.6 mg/kg BW). Median overall duration of toceranib phosphate treatment was 109 d (range: 21 to 469 d). In these 6 dogs, urine SG ranged from 1.014 to 1.034 (median: 1.032) at the time of drug discontinuation or death. None of these dogs received an omega-3 fatty acid supplement while receiving toceranib phosphate. Two of these six dogs received piroxicam concurrently with toceranib phosphate on TuThSaSu; 2 other dogs received concurrent prednisone or prednisolone at 0.5 mg/kg BW on TuThSaSu. One dog in this group had grade 1 proteinuria that remained stable for 135 d while the dog was receiving toceranib phosphate. This dog then died unexpectedly at home; her owners reported that she experienced disorientation, diarrhea, and labored breathing before death. This dog had been receiving toceranib phosphate with concurrent prednisone for a metastatic mast cell tumor. Physical examination and blood analysis evaluation 3 d before death had been unremarkable, and her UPC at that time was 0.8 (urine SG: 1.014). Grade 3 proteinuria was documented in the other 5 dogs, all of whom received enalapril at 0.5 mg/kg PO once or twice daily as treatment for their proteinuria. The BUN concentration and proteinuria did worsen in the dog with a BUN increase at baseline. After 83 d of treatment with toceranib phosphate and twice daily enalapril, BUN had increased from 16.1 to 29.6 mmol/L and UPC had increased from 2.3 to 5.7. Urine SG at this time was 1.012 and creatinine remained within the reference interval. This dog had concurrent progression of his urogenital transitional cell carcinoma. Due to a history of gastrointestinal intolerance, the dog was not receiving an NSAID as treatment for his cancer. In the remaining dogs, BUN and creatinine remained within reference intervals for the duration of toceranib phosphate treatment, although proteinuria worsened in 2 additional dogs. One of these dogs received toceranib phosphate for 190 d before the drug was discontinued due to a UPC of 6.3 (baseline: 2.7). This dog was diagnosed with hyperadrenocorticism 8 mo after toceranib phosphate was discontinued. The second of these dogs had a UPC of 1.6 (baseline: 1.0) detected after 469 d of treatment with toceranib phosphate; concurrent hypertension was also noted. Enalapril was increased to twice daily dosing and toceranib phosphate was discontinued due to progressive disease. In the remaining 2 dogs, proteinuria was stable for 21 and 50 d, at which time progressive disease occurred and toceranib phosphate was discontinued.

Discussion

In the present study, 12 of 49 dogs (24%) that were not proteinuric at baseline became proteinuric while receiving toceranib phosphate. Grade 1 elevations were most common. Even though 1 dog did develop proteinuria as early as 15 d after starting treatment, most dogs in our study did not become proteinuric until after the first month of therapy. Although the use of anti-inflammatory doses of glucocorticoids could have confounded our results, there was no association of glucocorticoid use with development of proteinuria ($P = 0.5$), perhaps because of the relatively low, infrequent doses dogs in our study received. Previous research by others showed that daily administration of higher doses of prednisone can cause proteinuria and glomerular changes in dogs (31). Concurrent NSAID use was also not associated with development of proteinuria ($P = 0.7$). This is also not entirely surprising. NSAID administration was intermittent, and renal toxicity from NSAIDs is typically an interstitial or tubular process, rather than glomerular (32–34).

We did find an association between duration of toceranib phosphate treatment and development of proteinuria ($P = 0.005$), with median treatment duration being longer in proteinuric dogs than non-proteinuric dogs. However, the median time to proteinuria in affected dogs was less than 2 mo, which is less than the median toceranib treatment duration of 112 d in the unaffected dogs. Therefore the association we detected does not indicate that dogs which receive toceranib phosphate for a long duration become proteinuric, but rather that development of proteinuria does not preclude long-term treatment with toceranib phosphate.

The clinical outcomes documented in our study population suggest proteinuria may be successfully managed clinically in some dogs receiving toceranib phosphate. Six of the 12 dogs that became proteinuric had their proteinuria resolve following temporary discontinuation of toceranib phosphate and reinstitution at a lower dose. Time to resolution was, however, variable. Many of the remaining affected dogs had stable UPC values until they were lost to follow-up or toceranib phosphate was discontinued for other reasons. One dog did have worsening proteinuria and onset of azotemia while receiving toceranib phosphate. This dog's initial UPC was high at 4.9 and there was not adequate follow-up to determine whether the abnormalities improved when toceranib phosphate was discontinued or whether proteinuria and azotemia could have contributed to the dog's death, which was attributed to progressive pulmonary anaplastic sarcoma.

We also found that the presence of proteinuria at baseline may not be a contraindication for toceranib phosphate treatment, although a study with a larger number of proteinuric dogs is necessary to make any definitive conclusions. The dogs in this group that did experience progression of their proteinuria had complicating factors of either disease progression or concurrent endocrinopathy. Most of the dogs with pre-existing proteinuria in our study did receive enalapril, an angiotensin-converting enzyme (ACE) inhibitor, concurrently, and this may have contributed to the outcomes we observed. A prospective study with an appropriate control group is warranted to determine whether therapies such as ACE inhibitors, omega-3 polyunsaturated fatty acids, or angiotensin II receptor blockade are indicated in all proteinuric dogs receiving toceranib phosphate. One dog with grade 1 proteinuria did die suddenly. As the clinical signs reported by her owners did not identify specific disease etiology (e.g., mast cell degranulation, pulmonary thromboembolism, disseminated intravascular coagulation, gastric dilatation, and volvulus), it is unknown to what degree treatment with toceranib phosphate may have contributed to her death.

One of the limitations of our study is its retrospective nature. Cancer is a known risk factor for proteinuria (35) and we did not have a control group of tumor-bearing dogs that did not receive toceranib phosphate. However, at baseline, only 6/55 dogs (11%) were proteinuric, compared to 18/55 dogs (33%) that were ultimately proteinuric by the end of our study. The fact that proteinuria tended to develop early on, and was associated with a longer median overall treatment duration, suggests the proteinuria that occurred in our study was unrelated to cancer progression in most dogs. An additional limitation of our study is that we included dogs with a variety of tumor types and different levels of disease burden, although most of the dogs were treated in the setting of macroscopic disease. This was done in an effort not to downsize the number of dogs that may have been affected by proteinuria. Finally, dogs in our study did not have uniform monitoring of systolic blood pressure measurements; therefore, we cannot comment on the role hypertension may have played in the development of proteinuria in affected dogs.

Given that we have documented that proteinuria can develop in dogs receiving toceranib phosphate, UA (with UPC if indicated), serum biochemistry panels, and blood pressure measurements should be performed before administration of toceranib phosphate and on a periodic basis thereafter. Further research is needed to determine whether proteinuria that develops in dogs receiving toceranib phosphate is associated with adverse consequences such as loss of urine concentrating ability, abnormalities in BUN, creatinine, symmetric dimethylarginine (SDMA), albumin, and anti-thrombin IIII concentrations, and/or clinical signs of protein-losing nephropathy. In addition to evaluating the role of ACE inhibitors and other renal-protective therapies, prospective studies are needed to identify risk factors for proteinuria, examine the role of hypertension, and develop optimal monitoring schedules.

Acknowledgments

The authors thank Francoise Vermeylen from the Cornell Statistical Consulting Unit (CSCU) for guidance in statistical analysis. Support for urine monitoring in some dogs was provided by a grant from the Daniel K. McIntosh Fund of the Toledo Community Foundation. CVJ

References

1. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172–187.
2. Takeuchi K, Ito F. Receptor tyrosine kinases and targeted cancer therapeutics. Biol Pharm Bull 2011;34:1774–1780.
3. Schlessinger J. Receptor tyrosine kinases: Legacy of the first two decades. Cold Spring Harb Perspect Biol 2014;6:ii a008912.
4. Rea D. Management of adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Ann Hematol 2015;94 Suppl 2: S149–158.
5. Shu M, Zai X, Zhang B, Wang R, Lin Z. Hypothyroidism side effect in patients treated with sunitinib or sorafenib: Clinical and structural analyses. PLoS One 2016;11:e0147048.
6. Abbas A, Mirza MM, Ganti AK, Tendulkar K. Renal toxicities of targeted therapies. Target Oncol 2015;10:487–499.
7. Hahn KA, Oglivie G, Rusk T, et al. Masitinib is safe and effective for the treatment of canine mast cell tumors. J Vet Intern Med 2008;22: 1301–1309.
8. London CA, Malpas PB, Wood-Follis SL, et al. Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision. Clin Cancer Res 2009;15:3856–3865.
9. Isotani M, Yamada O, Lachowicz JL, et al. Mutations in the fifth immunoglobulin-like domain of kit are common and potentially sensitive to imatinib mesylate in feline mast cell tumours. Br J Haematol 2010;148:144–153.
10. London C, Mathie T, Stingle N, et al. Preliminary evidence for biologic activity of toceranib phosphate (Palladia®) in solid tumours. Vet Comp Oncol 2012;10:194–205.
11. Robat C, London C, Bunting L, et al. Safety evaluation of combination vinblastine and toceranib phosphate (Palladia®) in dogs: A phase I dose-finding study. Vet Comp Oncol 2012;10:174–183.

12. Chon E, McCartan L, Kubicek LN, Vail DM. Safety evaluation of combination toceranib phosphate (Palladia®) and piroxicam in tumour-bearing dogs (excluding mast cell tumours): A phase I dose-finding study. Vet Comp Oncol 2012;10:184–193.
13. Bernabe LF, Portela R, Nguyen S, et al. Evaluation of the adverse event profile and pharmacodynamics of toceranib phosphate administered to dogs with solid tumors at doses below the maximum tolerated dose. BMC Vet Res 2013;9:190.
14. Pan X, Tsimbas K, Kurzman ID, Vail DM. Safety evaluation of combination CCNU and continuous toceranib phosphate (Palladia®) in tumour-bearing dogs: A phase I dose-finding study. Vet Comp Oncol 2016;14:202–209.
15. Harrington BK, Gardner HL, Izumi R, et al. Preclinical evaluation of the Novel BTK inhibitor Acalabrutinib in canine models of B-cell non-Hodgkin lymphoma. PLoS One 2016;11:e0159607.
16. Olmsted GA, Farrelly J, Post GS, Smith J. Tolerability of toceranib phosphate (Palladia®) when used in conjunction with other therapies in 35 cats with feline oral squamous cell carcinoma: 2009–2013. J Feline Med Surg 2017;19:568–575.
17. Merrick CH, Pierro J, Schleis SE, et al. Retrospective evaluation of toceranib phosphate (Palladia®) toxicity in cats. Vet Comp Oncol 2017;15: 710–717.
18. Harper A, Blackwood L. Toxicity and response in cats with neoplasia treated with toceranib phosphate. J Feline Med Surg 2017;19:619–623.
19. Pellin MA, Wouda RM, Robinson K, et al. Safety evaluation of combination doxorubicin and toceranib phosphate (Palladia®) in tumour bearing dogs: A phase I dose-finding study. Vet Comp Oncol 2017; 15:919–931.
20. London CA, Hannah AL, Zadovoskaya R, et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. Clin Cancer Res 2003; 9:2755–2768.
21. Tjostheim SS, Stepien RL, Markovic LE, Stein TJ. Effects of toceranib phosphate on systolic blood pressure and proteinuria in dogs. J Vet Intern Med 2016;30:951–957.
22. Brown MR, Cianciolo RE, Nabity MB, Brown CA, Clubb FJ, Lees GE. Masitinib-associated minimal change disease with acute tubular necrosis resulting in acute kidney injury in a dog. J Vet Intern Med 2013; 27:1622–1626.
23. Devine L, Polzin DJ. Presumed masitinib-induced nephrotic syndrome and azotemia in a dog. Can Vet J 2016;57:752–756.
24. Sum SO, Hensel P, Rios L, et al. Drug-induced minimal change nephropathy in a dog. J Vet Intern Med 2010;24:431–435.
25. Kandula P, Agarwal R. Proteinuria and hypertension with tyrosine kinase inhibitors. Kidney Int 2011;80:1271–1277.
26. Kamba T, Tam BY, Hashizume H, et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 2006;290:H560–576.
27. Sugimoto H, Hamano Y, Charytan D, et al. Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. J Biol Chem 2003;278:12605–12608.
28. Dubreuil P, Letard S, Ciufolini M, et al. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One 2009;4:7258.
29. Ischenko I, Guba M, Yezhelyev M, et al. Effect of Src kinase inhibition on metastasis and tumor angiogenesis in human pancreatic cancer. Angiogenesis 2007;10:167–182.
30. Veterinary cooperative oncology group — Common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol 2016;14:417–446.
31. Waters CB, Adams LG, Scott-Moncrieff JC, et al. Effects of glucocorticoid therapy on urine protein-to-creatinine ratios and renal morphology in dogs. J Vet Intern Med 1997;11:172–177.
32. Bergh MS, Budsberg SC. The coxib NSAIDs: Potential clinical and pharmacologic importance in veterinary medicine. J Vet Intern Med 2005;19:633–643.
33. Raekallio MR, Hielm-Björkman AK, Kejonen J, Salonen HM, Sankari SM. Evaluation of adverse effects of long-term orally administered carprofen in dogs. J Am Vet Med Assoc 2006;228:876–880.
34. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci 2013;16:821–847.
35. Cambier JF, Ronco P. Onco-nephrology: Glomerular diseases with cancer. Clin J Am Soc Nephrol 2012;7:1701–1712.