SOMETIMES OLD SCHOOL ISN’T COOL

There’s a Better Way to Scope...

Endo-i Wireless HD Endoscopes

- No Bulky Towers
- Easy to Transport
- 3 Models Available (1m, 1.5m, 3m)
- Tablet & App Included

**EASE-OF-USE**

**MANAGE PATIENT INFORMATION**

**EXPORT PROCEDURAL DATA**

EQ1510
1.5m, 10mm

Patented Technology

STERIS Animal Health
1.844.540.9810
sterisanimalhealth.com
An Open-label Phase 1 Dose-escalation Clinical Trial of a Single Intravenous Administration of Gemcitabine in Dogs with Advanced Solid Tumors

L. Marconato, R. Finotello, U. Bonfanti, M. Dacasto, L. Beatrice, S. Pizzoni, V.F. Leone, G. Balestra, T. Furlanello, C. Rohrer Bley, and L. Aresu

Background: A broad range of gemcitabine dosages have been used in dogs.

Hypothesis/Objectives: To determine maximally tolerated dose (MTD), dose-limiting toxicity (DLT), and preliminary antitumor activity of intravenous administration of gemcitabine in dogs with advanced solid tumors.

Animals: Twenty-two client-owned dogs.

Methods: Dogs with advanced cancer were prospectively enrolled in an open-label Phase 1 study of gemcitabine. Gemcitabine was administered as a 30-minute intravenous bolus at 800 mg/m², using escalation of 50 mg/m² increments with 3 dogs per dose level. MTD was established based on the number of dogs experiencing DLT assessed after 1 cycle. Treatment continued until disease progression or unacceptable toxicosis. Additional dogs were enrolled at MTD to better characterize tolerability, and to assess the extent and duration of gemcitabine excretion.

Findings: Twenty-two dogs were treated at 4 dose levels, ranging from 800 to 950 mg/m². Neutropenia was identified as DLT. MTD was 900 mg/m². DLT consisting of grade 4 febrile neutropenia was observed at 950 mg/m² in 2 dogs. There were no nonhematologic DLTs. Twenty dogs received multiple doses, and none had evidence of severe toxicosis from any of their subsequent treatments. At 900 mg/m², 2 complete and 5 partial responses were observed in dogs with measurable tumors. The amount of gemcitabine excreted in urine decreased over time, and was undetectable after the first 24 hours.

Conclusions and Clinical Importance: The recommended dose of gemcitabine for future Phase 2 studies is weekly 900 mg/m².

Key words: Canine; Dose-limiting toxicity; Gemzar; Maximally tolerated dose.

Gemcitabine is an antimetabolite analog to cytidine with unique metabolic and mechanistic properties. Preliminary studies conducted in dogs have shown a mild, schedule-dependent toxicity profile with a broad range of gemcitabine dosages (350–800 mg/m²).

Gemcitabine administered as single agent biweekly at dosages ranging from 300 to 675 mg/m² to dogs with various solid tumors was well-tolerated, with minimal toxicosis. In another study, when gemcitabine was administered to dogs with lymphoma at a dosage of 400 mg/m², treatment was either delayed or interrupted because of hematologic toxicoses, with no objective antitumor response. Gemcitabine used as single agent at the weekly dose of 800 mg/m² for the adjuvant treatment of mammary carcinoma caused grade 1 neutropenia in 4 of 61 treatments, and grade 1–2 gastrointestinal toxicosis in 2 of 61 treatments. Dogs with transitional cell carcinoma (TCC) of the urinary bladder treated with weekly gemcitabine at 800 mg/m² had a favorable toxicosis profile. Gemcitabine administered at 295–450 mg/m² weekly for 5 weeks to 15 dogs with hepatocellular carcinoma was associated with minimal toxicosis, but no survival advantage was demonstrated.

When considering the published literature, the absence of relevant hematologic and nonhematologic toxicoses is of particular interest, suggesting that substantial dose escalation might be possible in dogs with solid tumors.

Importantly, not only the dose, but also the duration of exposure of gemcitabine contributes to its cytotoxicity and, consequently, tolerability. Prolongation of the
infusion time in humans beyond 60 minutes increases toxicoses of gemcitabine.\(^8\) An infusion time ranging from 20 up to 60 minutes are used in dogs.\(^3\)-\(^7\)\(^9\)

Although gemcitabine has shown some antitumor activity in various canine solid tumors, its efficacy has not been fully determined yet. It is possible that treating dogs with gemcitabine at its maximally tolerated dose (MTD) might increase chances of efficacy. Indeed, it is well-known that underdosing of chemotherapeutic agents leads to reduced effectiveness and, consequently, to treatment failure. A phase 1 dose-escalation study to identify the MTD of gemcitabine in tumor-bearing dogs has not been performed so far. Given the low incidence of dose-limiting toxicity (DLT) when dogs received 800 mg/m\(^2\) of gemcitabine,\(^5\) it might be hypothesized that the MTD is likely higher.

The primary aim of this study was to complete a dose-escalation trial to determine MTD and DLT of gemcitabine when administered as a single IV dose infused over 30 minutes. Secondary endpoints were to assess the safety of repeated dosing and to obtain preliminary evidence of antitumor activity in dogs with advanced solid tumors. Finally, the gemcitabine amount in urine of treated dogs was monitored to provide safe handling guidelines.

**Materials and Methods**

**Dogs and Baseline Evaluation**

Client-owned dogs were enrolled in the study. Dogs were considered eligible to receive gemcitabine when they had an inoperable, recurrent, or metastatic solid tumor that had been confirmed histologically, and for which standard treatment options were not available or refused by the owners; an expected survival of at least 4 weeks without treatment; not received chemotherapy, immunotherapy, or radiotherapy for at least 4 weeks. Additional entry requirements included an adequate bone marrow, cardiac, renal, and hepatic function on day 0, as documented by a normal CBC, renal and hepatic serum chemistry values, thoracic auscultation and electrocardiogram. Specifically, dogs were required to have absolute neutrophil count (ANC) ≥1,500 cells/\(\mu\)L, hemoglobin ≥25%, platelet count ≥100,000/\(\mu\)L, serum creatinine concentration ≤2 times the upper limit of normal, lethargy/fatigue status (VCOG-CTCAE version 1.0) of either 0 or 1.\(^10\) Exclusion criteria included second malignancies, concurrent serious systemic diseases, body weight <10 kg and age <1 year. All owners signed an informed consent indicating their understanding of the investigational nature and risks of this study.

Baseline evaluation included physical examination, an electrocardiogram, a CBC with differential and platelet count, serum biochemical analysis, and urinalysis with microscopic examination of urine sediment. The dog’s vital signs and temperature were recorded before and after each injection of gemcitabine. Body weight was recorded on day 0 and 7. In case of hemolitic toxicosis, blood samples were collected daily after day 7 until recovery of neutrophil and platelet counts, whichever was longer.

Toxic effects were graded in accordance with VCOG-CTCAE guidelines.\(^10\) DLT was defined as any grade 3 adverse event, or grade 4 hematologic toxicosis that developed during a 7-day observation period. The MTD was defined as the highest dose level that resulted in a DLT in no more than one of 6 dogs.

**Dose Escalation**

This study was conducted as a prospective open-label phase I dose-escalation design that investigated the MTD and DLTs occurring over a 7-day period after a single IV dose of gemcitabine.\(^1\)

Handling and administration of gemcitabine, as well as disposal of related waste, were done according to guidelines on chemotherapy use in veterinary oncology.\(^12\)

Each dog received a first dose of gemcitabine as a 30 minute IV infusion. The initial dose was set at 800 mg/m\(^2\) on the basis of the results of previous studies showing good tolerability.\(^5\)\(^6\) Dose increases were evaluated in cohorts of 3 dogs. If none of the 3 treated dogs in a given cohort developed DLT after the 7 day assessment, the dose of gemcitabine for the next cohort was increased by 50 mg/m\(^2\). If one of the dogs developed DLT, an additional 3 dogs were treated at that dose; if no additional dogs developed DLT at that dose, the dose escalation was continued. If ≥2 dogs in a cohort developed DLT, no further dose escalations were performed and the MTD was considered exceeded. If a dog developed DLT, the dose was decreased by 1 dosage level for the following treatment.

Once MTD was established, escalation was stopped, and at least 3 additional dogs were treated with gemcitabine at that dose to further characterize any associated toxicosis and to characterize the extent of urinary excretion, leading to a minimum of 6 dogs treated at MTD. No intradog dose escalation was performed in this study.

Standard prophylactic anti-emetic treatment was provided (maropitant 2 mg/kg PO daily for 3 days) to all dogs. General symptom management and supportive care were provided as clinically indicated.

**Response to Therapy**

Gemcitabine was administered once weekly, and a minimum of 3 treatment cycles was required for a dog to be considered evaluable for antitumor response. Antitumor activity was assessed by standard criteria based on caliper or CT measurement evaluation, depending on tumor site.\(^13\) Response had to last for at least 28 days.

Dogs whose disease was responding or stable were offered to continue therapy for at least 6 cycles at the same dose level and schedule. Clients were allowed to remove their dog from the protocol in case of disease progression, other signs of compromised health, or in case of unacceptable toxicosis, at the discretion of the investigator, owner, or both.

**Urine Sampling and Determination of Gemcitabine Residues**

Once having finished the dose escalation and determined MTD, urine residues were monitored in 4 dogs treated at this dose. Urine samples (5 mL) were collected in 30 mL polypropylene tubes using voided urine at different time points. For 1 dog only, urine was sampled once daily in the morning starting 24 hours after administration gemcitabine until day 10 postinfusion. For the following 3 dogs, urine was sampled immediately before gemcitabine administration, and then 12 and 24 hours after the end of infusion. Samples were stored at −20°C until analysis.
A sensitive, selective, and quantitative method for the analysis of gemcitabine in urine samples was developed according to a previously described procedure. The samples were analyzed in ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC/MS-MS) operating in multiple reactions monitoring (MRM mode) in ESI positive. The UPLC/MS-MS variables were optimized and calibrated a wide concentration range (0.01–100 ng/mL). The recovery of gemcitabine was >85% with CV <3%.

**Statistical Analysis**

In keeping with Phase 1 trial design, no analyses were performed beyond simple descriptive statistics (eg, mean, median) for the population under study.

**Results**

**Animals**

Between July 2011 and December 2013, 22 dogs with various solid tumors were entered into this Phase 1 trial and received gemcitabine at 4 different dose levels: 3 dogs were enrolled in the 800 mg/m² cohort, 3 in the 850 mg/m² cohort, 13 in the 900 mg/m² cohort, and 3 in the 950 mg/m² cohort.

There were 10 mixed-breed dogs, 2 Pitt bull, 2 German Shepherd dogs, and 1 each of American Staffordshire Terrier, Cocker spaniel, Irish Terrier, Schnauzer, Dalmatian, Labrador retriever, Golden retriever, and Czechoslovakian wolf. There were 15 spayed females and 7 males (of which 5 neutered). Median age was 10 years (range, 6–13 years), and median weight was 27.9 kg (range, 14.2–39.1 kg).

Seventeen dogs had TCC involving the urinary tract, 4 dogs had a metastatic mammary carcinoma, and 1 dog had a lung carcinoma. Eighteen (82%) dogs had no prior treatment before the administration of gemcitabine, and had macroscopic tumors at the time of enrollment. The 4 dogs with mammary carcinoma underwent prior surgery; in all of them, the pathologist described the presence of neoplastic emboli and metastatic regional lymph nodes. Furthermore, 1 dog also had pulmonary metastases. These 4 dogs were treated with gemcitabine in the adjuvant setting.

None of the dogs had received previous chemotherapy and no comorbidities were identified.

**Determination of MTD and DLT**

All dogs were used for toxicity assessment evident after 1 gemcitabine administration. Table 1 shows the results of hematologic and nonhematologic toxicoses by dose level for each dog at that dose.

A total of 131 drug administrations have been given with doses ranging from 800 to 950 mg/m² and with a median of 6 cycles per dog (range, 1–25). No death caused by treatment-related toxicoses occurred. Overall, neutropenia was identified as the dose-limiting toxic event. Table 2 displays the median nadir of the ANC, packed cell volume, hemoglobin, and platelets by cohort. Neutropenia of some degree was recognized in 11 of the 22 dogs tested (50%), and in all 11 dogs the neutropenia was identified 1 week after treatment.

Gemcitabine was administered at 800, 850, and 900 mg/m² for the first 3 cohorts. None of the 3 dogs enrolled in each of these cohorts experienced a DLT. One of 3 dogs at 850 mg/m² had grade 1 nonfebrile neutropenia and anemia, and 1 of these had grade 2 nonfebrile neutropenia and grade 1 anemia. At 900 mg/m² 2 of 3 dogs experienced grade 1 nonfebrile neutropenia, 1 dog experienced grade 1 anemia, and 1 of these had grade 1 gastrointestinal toxicity, consisting of loss of appetite and nausea.

Of the 3 dogs that were enrolled in the subsequent 950 mg/m² cohort, 2 experienced a DLT consisting of febrile grade 4 neutropenia. Both dogs were hospitalized, received intravenous administration of antibiotics, and recovered after 1 week with no prolonged neutropenia. One of these dogs was withdrawn from the

### Table 1. Hematologic and nonhematologic toxicoses by dog and dose level following administration of a single dose of gemcitabine.

| Dose (mg/m²) | No. of Dogs | No. of Courses | BM Toxicoses, Grade (no. of dogs) After 1 Course | Gastrointestinal Toxicoses, Grade (no. of dogs) After 1 Course |
|--------------|-------------|----------------|-----------------------------------------------|-------------------------------------------------------------|
| 800          | 3           | 43             | 0 (3)                                         | 0 (2), 1 (1)                                                |
| 850          | 3           | 22             | 0 (1), 1 (1), 2 (1)                            | 0 (1), 2 (2)                                                |
| 900          | 13          | 61             | 0 (7), 1 (5), 2 (1)                            | 0 (10), 1 (3)                                               |
| 950          | 3           | 5              | 2 (1), 4 (2)                                  | 0 (1), 2 (2)                                                |

### Table 2. Hematologic toxicity among the first treatment cycle.

| Dose (mg/m²) | Median ANC/µL (range) | Median Hgb (g/dL) (range) | Median PCV (range) | Median Platelets × 10⁹/µL (range) |
|--------------|-----------------------|----------------------------|--------------------|----------------------------------|
| 800          | 3,900 (3,200–5,600)   | 14.2 (13.1–14.6)           | 51 (49–52)         | 265 (230–370)                   |
| 850          | 1,600 (1,400–8,200)   | 10.9 (10.8–11.7)           | 41 (41–44)         | 147 (117–228)                   |
| 900          | 5,400 (1,002–10,700)  | 13.1 (10.5–18.5)           | 43.1 (35–53)       | 271 (120–577)                   |
| 950          | 300 (280–1,001)       | 12.8 (11.4–13.0)           | 40 (37–52)         | 289 (174–345)                   |

Hg, hemoglobin.
Responses to gemcitabine in 16 dogs with macroscopic tumors having received at least 3 doses of gemcitabine.

| Cohort (mg/m²) | No. of Dogs | Type of Tumor                      | CR | PR | SD | PD |
|---------------|-------------|-----------------------------------|----|----|----|----|
| 800           | 3           | TCC (3)                           | 0  | 2  | 1  | 0  |
| 850           | 3           | TCC (3)                           | 0  | 3  | 0  | 0  |
| 900           | 9           | TCC (7), mammary carcinoma (1), lung carcinoma (1) | 2  | 6  | 1  | 0  |
| 950           | 1           | TCC (1)                           | 0  | 0  | 1  | 0  |

PD, progressive disease.

Cumulative Dosing

Twenty dogs received multiple doses of gemcitabine: 3 dogs were in the 800 mg/m² cohort and received 8, 10, and 25 doses on a weekly basis; 3 dogs were in the 850 mg/m² cohort and received 5, 6, and 11 doses; 13 dogs were in the 900 mg/m² cohort and received 2, 3 (n = 2), 4 (n = 4), 6 (n = 5), and 7 (n = 1) doses; and 1 dog was in the 950 mg/m² cohort and received 3 doses. The intradog dosage of gemcitabine was kept constant for these 20 dogs. Overall, none of the dogs receiving multiple treatments on a weekly basis experienced severe toxicosis from any of their subsequent treatments, demonstrated by clinical history and CBCs performed 1 week after all additional treatments.

Clinical Response and Antitumor Activity

Eighteen dogs were available for clinical response after 1 dose of gemcitabine. Among them, 13 dogs with urinary TCC and 1 dog with pulmonary carcinoma experienced clinical improvement. Three dogs with urinary TCC were stable, whereas 1 dog with urinary TCC had worsened clinical signs.

Four dogs had microscopic disease at baseline and no clinical signs; therefore, these dogs were not assessable for gemcitabine-induced clinical benefit.

Responses could not be ascertained for 3 dogs, which did not complete 3 cycles of treatment, whereas 19 dogs (16 dogs with macroscopic tumors and 3 dogs with microscopic tumors) having received at least 3 cycles of gemcitabine were available for tumor response.

Among the 16 dogs with measurable tumors, 2 achieved complete remission (CR) (1 dog with pulmonary metastases from a mammary carcinoma, 1 TCC), 11 dogs with TCC achieved partial remission (PR), and 3 dogs achieved SD (2 TCC and 1 lung carcinoma), for an overall response rate in the macroscopic setting of 88.9% (Table 3). Among responding dogs, median duration of response was 262 days (range, 42–1,784 days).

Three dogs with surgically removed metastatic mammary carcinoma and neoplastic emboli did not progress during the study period, 65, 209, and 405 days after enrollment.

All CR (including the 3 dogs with microscopic disease) were observed at the 900 mg/m² dose level. PR were documented at the following dose levels: 800 mg/m² (n = 2), 850 mg/m² (n = 3), and 900 mg/m² (n = 6).

All responding dogs continued to receive gemcitabine treatment until completion of six or more planned courses (n = 6), treatment change (n = 5), or tumor progression (n = 5).

Gemcitabine Levels in Urine

Gemcitabine levels were determined in 19 urine samples collected at several time points before and after the administration of chemotherapy in 4 dogs treated at the MTD. After 12 hours, the gemcitabine concentration was 4.1, 1.26, 1.84, and 1.78 ng/mL respectively. For all dogs, it was impossible to recover any residue after 24 hours after administration of gemcitabine.

Discussion

Previous experience with single-agent gemcitabine administered at different dosing and schedule options to dogs with tumors other than lymphoma was encouraging; therefore the current Phase 1 clinical trial was conducted to determine MTD and DLT.

Doses and schedule adopted in former clinical trials included gemcitabine administered at 300–675 mg/m² every 2 weeks,3 weekly 800 mg/m²3,5,6 and weekly 350–400 mg/m²7 with a good safety profile, suggesting that substantial dose escalation might be possible. Indeed, in the present study, the MTD for gemcitabine administered...
as a 30-minute infusion to chemotherapy-naïve dogs with advanced solid tumors was weekly 900 mg/m².

Dose escalation on this study was planned in a traditional manner with a minimum of 3 dogs to be entered at each dose level. No new dogs were to receive an escalated dose until all dogs at the current dose level had been observed for a minimum of 7 days. At 900 mg/m², the major toxicities were grade 2 short-lived neutropenia and transient nausea and vomiting. Gemcitabine was otherwise well-tolerated in all of the dogs developing grade 3–4 neutropenia or further adverse effects. Importantly, there were no deaths with this dosage, and no related life-threatening complications.

There were two cases of DLT when gemcitabine was administered at 950 mg/m², consisting of grade 4 febrile neutropenia, which was not seen in any other dogs treated at lower dosages. Both DLTs recovered after hospitalization and symptomatic treatment; their neutrophil counts were within normal limits 14 days after dosing.

Notably, of the 20 dogs that received ≥3 gemcitabine treatments, none had any clinically relevant decrease in neutrophils, hematocrit, hemoglobin or platelet count over time, suggesting that neutropenia was not cumulative, and that gemcitabine might not irreversibly damage hematopoietic cells.

In contrast with the toxicoses observed in our study, dogs with lymphoma treated with gemcitabine at 400 mg/m² experienced severe hematologic toxicoses, which is much lower than the MTD found here. This discrepancy might be attributable to the systemic nature of lymphoma. Indeed, approximately 20% of the dogs in that study had bone marrow involvement, possibly explaining the occurrence of grade 3 (9%) or 4 (5%) neutropenia.

Gemcitabine is an effective agent in the treatment of many human tumors. Although efficacy was not a primary endpoint of this trial, we found preliminary evidence of antitumor activity after a single-dose administration as well as evidence of a dose response. When treated at the gemcitabine MTD on a weekly basis, all 7 dogs with TCC responded to treatment (1 CR and 6 PR), and none progressed. Although quite unexpected, these results should not be surprising, as there is substantial evidence that dose-intensity is an important determinant of outcome in the treatment of solid tumors with cytotoxic chemotherapy. It is possible that administering gemcitabine at MTD might have maximized activity, leading to a better response rate compared with the same drug administered at a lower dose.

Furthermore, all 4 dogs with metastatic mammary carcinoma did not progress and among them, 1 dog with lung metastases experienced CR, as demonstrated by follow-up CT. Notably, because response was evaluated after only 3 doses of gemcitabine, responses might be further improved by additional cycles.

The presence of chemotherapy residues in dogs’ urines might represent an exposure hazard for owners and other animals sharing the same environment. Previous studies have attempted to measure urine residues of vincristine, vinblastine, cyclophosphamide, doxorubicin, and carboplatin. Urine residues of gemcitabine were detectable in treated dogs immediately after the administration. However, after 24 hours, drug residues in urine were below the limits of detection with trace concentrations only measurable in single samples, indicating that after 24 hours the urine might be considered free of exposure hazard. Even though gemcitabine metabolites were not measured, these are thought to be inactive in humans, thereby not being relevant for environmental contamination.

Limitations of the current study are the small population and the varied dose-intensity cohorts. Despite the good toxicity profile and the encouraging observed response rates in dogs with TCC, we acknowledge that larger more appropriately powered disease-specific studies are needed to more carefully characterize the efficacy of gemcitabine administered at its MTD. Also, whether a higher cumulative dose translates into higher response rates will need to be further evaluated.

In conclusion, therapeutic doses associated with efficacy of gemcitabine monotherapy were achieved. The safety and preliminary efficacy results of this study suggest that the weekly 900 mg/m² schedule is suitable for further exploration in Phase 2 clinical trials focused on dogs with TCC.

Footnote

a Cerenia, Zoetis, Rome, Italy

Acknowledgment

Conflict of Interest Declaration: Authors disclose no conflict of interest.

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

References

1. Heinemann V, Xu YZ, Chubb S, et al. Cellular elimination of 2',2'-difluorodeoxycytidine 5'-triphosphate: A mechanism of self-potentiation. Cancer Res 1992;52:533–539.
2. Plunkett W, Huang P, Xu YZ, et al. Gemcitabine: Metabolism, mechanisms of action and self-potentiation. Semin Oncol 1995;22:3–10.
3. Kosarek CE, Kisseberth WC, Gallant SL, et al. Clinical evaluation of gemcitabine in dogs with spontaneously occurring malignancies. J Vet Intern Med 2005;19:81–86.
4. Turner AI, Hahn KA, Rusk A, et al. Single agent gemcitabine chemotherapy in dogs with spontaneously occurring lymphoma. J Vet Intern Med 2006;20:1384–1388.
5. Marconato L, Lorenzo RM, Abramo F, et al. Adjuvant gemcitabine after surgical removal of aggressive malignant mammary tumours in dogs. Vet Comp Oncol 2008;6:90–101.
6. Marconato L, Zini E, Lindner D, et al. Toxic effects and antitumor response of gemcitabine in combination with piroxicam treatment in dogs with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 2011;238:1004–1010.
7. Elpiner AK, Brodsky EM, Hazzah TN, et al. Single-agent gemcitabine chemotherapy in dogs with hepatocellular carcinomas. Vet Comp Oncol 2011;9:260–268.
8. Abbruzzese JL. Phase I studies with the novel nucleoside analog gemcitabine. Semin Oncol 1996;23:25–31.
9. Freise KJ, Martin-Jimenez T. Pharmacokinetics of gemcitabine and its primary metabolite in dogs after intravenous infusion. J Vet Pharmacol Ther 2006;29:147–152.
10. Veterinary cooperative oncology group. Veterinary cooperative oncology group—common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. Vet Comp Oncol 2004;2:194–213.
11. Vail DM. Cancer clinical trials: Development and implementation. Vet Clin North Am Small Anim Pract 2007;37:1033–1057.
12. Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine, 2nd ed. European College of Veterinary Internal Medicine of Companion Animals; 2007. Available at: http://www.ecvim-ca.org. Accessed August 15th, 2014.
13. Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): A Veterinary Cooperative Oncology Group (VCOG) consensus document. Vet Comp Oncol 2013; Accessed August 15, 2014. doi: 10.1111/vco.12032. [Epub ahead of print]
14. Mendu DR1, Soldin SJ. Simultaneous determination of levetiracetam and its acid metabolite (ucb L057) in serum/plasma by liquid chromatography tandem mass spectrometry. Clin Biochem 2010;43:485–489.
15. Dodwell DJ, Gurney H, Thatcher N. Dose intensity in cancer chemotherapy. Br J Cancer 1990;61:789–794.
16. Janssens T, Brouwers EE, de Vos JP, et al. Inductively coupled plasma mass-spectrometric determination of platinum in excretion products of client-owned pet dogs. Vet Comp Oncol doi:10.1111/vco.12025.
17. Knobloch A, Mohring SA, Eberle N, et al. Cytotoxic drug residues in urine of dogs receiving anticancer chemotherapy. J Vet Intern Med 2010;24:384–390.
18. Lokiec F, Lansiaux A. Gemcitabine: De la prélincé à la clinique en passant par la pharmacocinétique. Bull Cancer 2007;94:S85–89.