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Original Article

# Evaluation of carboplatin sustained-release delivery system in dogs with cancer

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**Abstract**

The objective of the study was to assess the carboplatin sustained-release (CSR) as an injectable, biodegradable polymer system designed to uniformly release carboplatin over 30 days at a dose of 350 mg $m^{-2}$. The study involved seven client-owned dogs with histologically or cytologically confirmed neoplasia that were treated with CSR intramuscularly. Platinum levels were measured at days 0, 7, 14, 21 and 28. Complete blood cell (CBC) counts, body weight, local toxicity and side effects were also evaluated at the time of platinum measurement at days 0, 7, 14, 21 and 28. CSR released carboplatin steadily over 30 days. Neutropenia was noted as Grade 3 in one dog (14%) and Grade 4 in two dogs (29%) at day 14, and Grade 4 in one dog (14%) at day 21. Thrombocytopenia was noted as Grade 2 in four dogs (57%), Grade 3 in one dog (14%) and Grade 4 in one dog (14%) at day 14; Grade 2 in two dogs (29%) and Grade 3 in one dog (14%) at days 21 and 28. Grade 1 lethargy in one dog (14%) and Grade 1 nausea in dog (14%) occurring within 7 days after administration. No obvious local injection site reactions were noted. CSR administered at 350 mg $m^{-2}$ intramuscularly resulted in a steady release over 30 days. Myelosuppression (Grade 4) was noted in 86% of patients. CSR released the drug slowly and steadily, however additional studies are needed to assess acceptable dosage requirements.

*Keywords:* carboplatin, canine, sustained-release, chemotherapy, toxicity.

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## Introduction

Carboplatin, diammine [1,1-cyclobutane-dicarboxylate(2-)-0,0′]-(SP-4-2) platinum (II), is an antineoplastic alkylating agent used to treat a variety of neoplastic diseases in cats and dogs. These diseases include but are not limited to squamous cell carcinoma, pleural adenocarcinomas, nasal carcinomas, thyroid adenocarcinomas, osteogenic sarcomas, urinary transitional cell carcinomas and malignant melanomas (Page *et al.* 1993; Chun *et al.* 1997, 2007; Hahn *et al.* 1997; Bailey *et al.* 2003, 2004; Kisseberth *et al.* 2008; Rassnick *et al*. 2001). Carboplatin is a cell-cycle non-specific platinum compound that is intracellularly activated to form reactive platinum complexes that bind to nucleophilic groups. These complexes interact with intra-strand and inter-strand DNA to cause strand cross-linkage, thus inhibiting DNA replication, RNA transcription and protein translation (Reed 2006). After intravenous (i.v.) administration, carboplatin is well distributed throughout the body, with the highest concentrations found in the liver, kidney, skin and tumour tissue (Elferink *et al.* 1987; Reed 2006). It is excreted in the urine within 24 h of administration, with approximately 70% of the administered platinum secreted in the urine after 72 h. The clearance of carboplatin is predicted by creatinine clearance, and the dose relationship compared to renal function is used to predict the dose required to achieve the desired plasma area under the curve (AUC) (Elferink *et al.* 1987; Calvert *et al.* 1989; Theon *et al.* 1996; Chatelut *et al.* 2000).



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The limitations of intravenous chemotherapy include adverse systemic effects, such as myelosuppression, inadequate and fluctuating drug concentrations in the plasma for the desired therapeutic effect as well as the need for larger doses due to the lack of susceptibility of neoplastic cells (Elferink *et al.* 1987; Page *et al.* 1993; Hahn *et al.* 1997; Phillips 1999; Reed 2006; Kisseberth *et al.* 2008).

Sustained-release (SR) delivery systems utilize injectable, biodegradable microspheres for subcutaneous or intramuscular administration of chemotherapy (Kitchell *et al.* 1995; Gavini *et al.* 2005; Manunta *et al.* 2005; Dunn *et al*. 1996), opioids (Nunamaker *et al.* 2013; Chum *et al.* 2014) and non-steroidal anti-inflammatory drugs (NSAID) (Bauer *et al.* 2014). SR delivery systems have been shown to have a prolonged release and duration of effect (Nunamaker *et al.* 2013; Bauer *et al.* 2014; Chum *et al.* 2014), with little to no evidence of local or systemic toxicity (Kitchell *et al.* 1995; Gavini *et al.* 2005; Manunta *et al.* 2005; Nunamaker *et al.* 2013; Bauer *et al.* 2014; Chum *et al.* 2014). They have enhanced the dispersibility and syringeability of drug formulations while allowing for a broader therapeutic range without long-term toxicity (Kitchell *et al.* 1995; Gavini *et al.* 2005; Manunta *et al.* 2005) (Nunamaker *et al.* 2013; Bauer *et al.* 2014; Chum *et al.* 2014).

In this investigation, a proprietary, biodegradable polymer designed for the sustained-release of carboplatin (CSR) was evaluated. The matrices for CSR are formulated from a safe, reliable biodegradable polymer, which are eliminated via the tricarboxylic acid cycle as carbon dioxide and water. These matrices were the same as those used to formulate buprenorphine SR (Nunamaker *et al.* 2013; Chum *et al.* 2014) and Meloxicam SR (Bauer *et al.* 2014). The drug was intramuscularly administered to dogs with various types of cancer.

The hypothesis was that CSR would release the drug over a 4-week period at a dose of 350 mg $m^{-2}$.

## Materials and methods

### Subjects and pre-treatment evaluation

This study involves seven client-owned dogs with cytologically or histologically confirmed malignancies between June 2009 and June 2010, and was approved by the Institutional Review Board and the Institutional Animal Care and Use Committee (IACUC). Each dog was initially assessed by reviewing the history, physical examination, tumour measurement, lymph node measurement, pathologic confirmation of the malignancy, prior blood work, current complete blood cell count (CBC) and serum chemistry panel.

Dogs were excluded from the study if they were cachectic or had received any chemotherapy, exogenous steroids or anaesthesia in the 30 days before initial presentation at the clinical site.

### Investigational agent

Carboplatin sustained-release was supplied in a 100 mg $mL^{-1}$ suspension of carboplatin in a proprietary liquid polymer delivery system (SR Veterinary Technologies, Windsor, CO). The polymer consisted of poly(DL-lactide-co-caprolactone) dissolved in *N*-methyl-2-pyrrolidone to achieve an injectable viscosity. Molecular weight was determined by gel permeation chromatography with multi-angle light-scattering detector (GPC-MALS). Carboplatin powder was suspended in the liquid polymer system to produce 100 mg $mL^{-1}$ concentration test formulation. A 2-mL drug suspension and polymer system were loaded into 3 cc syringes, then capped and placed in a foil-lined package with a 3 cc mixing or re-suspension syringe. The sealed package was then sterilized by gamma irradiation. The polymer released carboplatin over 30 days.

The CSR injection was calculated at a dose of 350 mg $m^{-2}$ and intramuscularly administered in the epaxial musculature. Under the direction of the attending clinician, 0.1 mg $kg^{-1}$ i.v. butorphanol (butorphanol tartrate – 10 mg $mL^{-1}$, Merck Animal Health, Summit, NJ) per dog was administered as an analgesic for the possible pain associated with the CSR injection. The injection site for CSR was shaved and sterilized prior to the CSR injection. Appropriate biosafety precautions were implemented when preparing and administering the CSR, including the use of latex, powder-free gloves, protective gowns and eyewear.

### Platinum quantification

Serum samples for platinum analysis were sampled weekly after CSR was administered. Six millilitres of blood was obtained, centrifuged and the resultant plasma was placed into heparinized blood collection tubes that were then frozen at 0°F (−18°C) to determine serum platinum levels by mass spectroscopy. The platinum concentrations were quantified using inductively coupled plasma mass spectroscopy (ICP-MS). A quality control (QC) test sample was analysed with every five samples. Test materials were diluted in screw-cap Teflon tubes on a heat block at 90°C for 2 h. The plasma samples were digested in an equivalent volume of trace mineral grade nitric acid. The plasma digests were diluted in the ratio 1:10 with 18.2 MOhm ultrapure water to a 5% nitric acid matrix prior to analysis. The plasma analysis results are reported on a wet weight basis. This method resulted in a matrix match to the standards and QC samples. Prepared samples that showed higher mineral content than the high standard were diluted in the ratio 1:10 in 5% nitric acid and re-analysed. The standard curves consisted of five concentrations between 10 and 500 ng $mL^{-1}$. The QC sample had to be ± 5% of the known platinum specifications to pass. Any group of samples that yielded a failed QC test was re-analysed.

### Efficacy and safety evaluations

The following variables were serially monitored over the 4-week period: packed cell volume (PCV), white blood cell count (WBC), neutrophils and platelets (PLTs). In addition, local toxicity and systemic side effects were noted at the time of each evaluation following administration of CSR. The total granulocyte count was assessed separately from the total white cell count. Side effects were noted in the medical history obtained from owners and based on the physical examination, body weight measurement and clinicopathological data. The haematological and other toxic effects were graded in accordance with the Veterinary Co-operative Oncology Group (VCOG, 2004) Common Terminology Criteria for Adverse Events. Side effects were noted in the medical history obtained from owners and based on the physical examination, body weight measurement and clinicopathological data.

## Results

Ten dogs were enrolled in this study and seven dogs completed the 4-week follow-up. Breeds included were mixed breed ($n$ = 4), Golden Retriever ($n$ = 1), Labrador Retriever ($n$ = 1) and Border collie ($n$ = 1). There were five spayed females and two neutered males. The median age was 10 years (range 7–13 years) and median weight was 30.9 kg (range 17.2–47 kg).

Tumour types included melanoma ($n$ = 3), transitional cell carcinoma ($n$ = 2), osteosarcoma ($n$ = 1) and trichoepithelioma ($n$ = 1).

### Platinum determination

The diffusion of CSR in tissues and the time of drug release were evaluated based on the platinum concentration in the plasma over 28 days (Table 1). The dogs were evaluated at the pre-treatment physical examination and each week for an additional 4 weeks. Platinum concentrations were detectable in all seven dogs, with a steady and gradual decline over the course of 28 days.

**Table 1.** Plasma concentration in PPM released over 28 days after intramuscular injection of carboplatin sustained-release (CSR) at 350 mg $m^{-2}$

| Dog | Carboplatin concentration (PPM) | | | | |
|---|---|---|---|---|---|
| | Day 0 | Day 7 | Day 14 | Day 21 | Day 28 |
| 1 | <0.002 | 0.499 | 0.274 | 0.156 | 0.103 |
| 2 | <0.002 | 0.36 | 0.194 | 0.126 | 0.095 |
| 3 | <0.002 | 0.757 | 0.268 | 0.164 | 0.108 |
| 4 | <0.002 | 0.352 | 0.217 | 0.118 | 0.095 |
| 5 | <0.002 | 0.626 | 0.341 | 0.196 | 0.135 |
| 6 | <0.002 | 0.578 | 0.23 | 0.156 | 0.127 |
| 7 | <0.002 | 0.28 | 0.116 | 0.061 | 0.044 |
| Mean carboplatin level (PPM) | <0.002 | 0.499 | 0.23 | 0.156 | 0.103 |

### Toxicities

Weekly haematology results with CSR administration are reported in Table 2.

Constitutional clinical signs included Grade 1 lethargy in one dog (14%) and Grade 1 nausea in dog (14%) occurring within the first 7 days after administration. No local injection site reactions were noted.

## Discussion

Slow release chemotherapy using cisplatin has been evaluated in canine nasal tumours (Lana *et al.* 1997), soft tissue sarcomas (Dernell *et al.* 1997), osteosarcoma (Withrow *et al.* 1995) and squamous cell carcinomas (Kitchell *et al.* 1995). Carboplatin chemotherapy, an analogue of cisplatin, has been used in a variety of tumours as an intravenous or intracavitary injection. The extended exposure of cells to a cytotoxic drug at an adequate concentration is critical to achieve effectiveness. The half-life of carboplatin is approximately 60 min in dogs (Gaver *et al.* 1988) when injected intravenously, and this drug is undetectable 24 h after injection (Page *et al.* 1993).

This study revealed that CSR, when administered as an intramuscular injection, slowly releases carboplatin over 30 days. When compared to baseline levels at day 0, the highest concentration of CSR was noted at day 7 and declined by 46% by day 14. At day 21, the PPM dropped by 69% and at day 28 dropped to 79%. Platinum levels were not evaluated past day 28. As there was still detectable drug at day 28, additional studies are needed to evaluate the duration of time CSR persists in serum thus allowing for more accurate dosing intervals and assessment of possible cumulative toxicity. In addition, preliminary PK data are not yet available and would need to be evaluated prior to moving forward with a phase I clinical trial.

Mass spectrometry methods tend to be highly sensitive and are the standard method for determining

**Table 2.** Haematological evaluation and toxicity at day 0 (baseline) and days 7, 14, 21 and 28 following carboplatin sustained-release (CSR) administration at 350 mg $m^{-2}$

| Dog | 1 | 2 | 3 | 4 | 5 | 6 | 7 | % Toxicity |
|---|---|---|---|---|---|---|---|---|
| White blood cell count $10^3$ | | | | | | | | |
| Day 0 | 7.5 | 8.2 | 5 | 7.7 | 4.27 | 9.82 | 6.93 | 0 |
| Day 7 | 5.3 | 6.3 | 3.8 | 5.2 | 4.26 | 8.76 | 2.77 | 0 |
| Day 14 | 6 | 7.5 | 0.5 | 8.1 | 1.35 | 6.92 | 1.01 | 14 |
| Day 21 | 4.5 | 5.8 | 5.3 | 3.7 | 0.69 | 15.61 | 4.76 | 14 |
| Day 28 | 8.7 | 13.1 | 8.4 | 10.1 | 2.48 | 11.66 | 9.88 | 0 |
| Granulocyte count $10^3$ | | | | | | | | |
| Day 0 | 5.6 | 5.3 | 3.8 | 6.1 | 3.07 | 7.1 | 4.25 | 0 |
| Day 7 | 4.1 | 4.2 | 3 | 3.7 | 3.02 | 6.21 | 1.88 | 0 |
| Day 14 | 4.1 | 4.8 | 0.1 | 6.6 | 0.62 | 4.73 | 0.06 | 43 |
| Day 21 | 3.2 | 2.3 | 3.5 | 2.3 | 0.19 | 11.83 | 2.81 | 14 |
| Day 28 | 4.8 | 6.7 | 6.7 | 8.3 | 1.77 | 8.81 | 7.21 | 0 |
| Packed cell volume (%) | | | | | | | | |
| Day 0 | 45 | 42 | 49 | 45 | 58.6 | 41.6 | 37.6 | 0 |
| Day 7 | 43 | 44 | 44 | 42 | 59.4 | 45.8 | 37.2 | 0 |
| Day 14 | 41 | 42 | 40 | 44 | 49.4 | 41.2 | 29.6 | 14 |
| Day 21 | 40 | 42 | 40 | 35.3 | 44.8 | 39 | 32.4 | 0 |
| Day 28 | 42 | 40 | 41 | 40 | 42 | 37 | 41 | 0 |
| Platelet count $10^3$ | | | | | | | | |
| Day 0 | 305 | 293 | 231 | 343 | 133 | 342 | 277 | 0 |
| Day 7 | 223 | 291 | 214 | 287 | 137 | 312 | 194 | 0 |
| Day 14 | 59 | 123 | 45 | 75 | 8 | 88 | 65 | 86 |
| Day 21 | 323 | 361 | 514 | 304 | 46 | 491 | 383 | 14 |
| Day 28 | 254 | 85 | 692 | 431 | 54 | 700 | 639 | 14 |

platinum levels in plasma and serum (ICH Q2 (R1), 2005). The QC sample was analysed every five test samples, thus the method and analysis appear to be accurate, despite the lack of any pre-clinical or in vitro data available for this particular polymer system. According to the ICH requirements, this study did adhere to guidelines with the assay qualification; however, pre-clinical and in vitro data would need to be tested – should this product move forward in additional clinical trials.

The clinical dose of carboplatin as an i.v. injection is 300 mg $m^{-2}$, however this study utilized a higher dose of 350 mg $m^{-2}$. The haematological toxicity overall was highest at day 14 with thrombocytopenia noted in six (86%) out of seven dogs and neutropenia noted in three (43%) out of seven dogs. The two smallest dogs appeared to experience the highest grade haematological toxicity that persisted over 2 weeks. Smaller dogs may experience increased toxicity with body surface area dosing (Ogilvie *et al.* 1989; Frazier & Price 1998; Price & Frazier 1998, 1998), so more thorough drug dosing studies are needed to assess therapeutic requirements while minimizing haematological toxicity.

Three dogs that did not complete the study all experienced progressive disease and were euthanized.

Several limitations were noted in this study, including an overall small number of dogs enrolled and lack of a homogenous cancer population. Assessment of renal function with urinalysis and serum BUN/creatinine at baseline and weekly after administration would also be ideal as platinum agents are nephrotoxic, although no dogs in the study showed evidence of renal failure during the study period.

Due to its low oral bioavailability, additional routes of administration and delivery systems are being explored to help increase the exposure of cancer cells to cytotoxic amounts of carboplatin. The results showed that CSR was slowly released over 4 weeks. Additional studies are needed to assess efficacy, safety and dosage requirements.

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## Source of funding

SR Veterinary Technologies (3rd author) arranged for platinum testing at University of Utah. SR Vet is the company that made the drug and thus paid for the platinum testing. Clients were not paid for enrollment.

## Conflict of interest

The authors declare that they have no conflicts of interest.

## Contributions

Dr. Tansey is primary author, Dr. Zwahlen was a senior clinician in the study and mentor to Dr. Tansey through her residency. Steven Kirschner provided the drug and platinum testing levels at SR Veterinary Technologies. Dr. Nakamura assisted with the writing, statistical analysis and editing of the manuscript.

## References

Bailey D.B., Erb H.N., Williams L., Ruslander D. & Hauck M. (2003) Carboplatin and Doxorubicin Combination chemotherapy for the treatment of appendicular osteosarcoma in the dog. *Journal of Veterinary Internal Medicine* **17**, 199–205.

Bailey D.B., Rassnick K.M., Erb H.N., Dykes N.L., Hoopes J. & Page R.L. (2004) Effect of glomerular filtration rate on clearance and myelotoxicity of carboplatin in cats with tumors. *American Journal of Veterinary Research* **65**(11), 1502–1507.

Bauer C., Frost P. & Krischner S. (2014) Pharmacokinetics of 3 Formulations of Meloxicam in Cynomolgus Macaques (*Macaca fascicularis*). *Journal of the American Association for Laboratory Animal Science* **53**, 1–10.

Calvert A.H., Newell D.R., Gumbrell L.A., O'Reilly S., Burnell M., Boxall F.E. *et al.* (1989) Carboplatin dosage:

prospective evaluation of a simple formula based on renal function. *Journal of Clinical Oncology* **7**, 1748–1756.

Chatelut E., Pivot X., Otto J., Chevreau C., Thyss A., Renée N. *et al.* (2000) A limited sampling strategy for determining Carboplatin AUC and monitoring drug dosage. *European Journal of Cancer* **36**, 264–269.

Chum H.H., Jampachairsri K., McKeon G.P., Yeomans D.C., Pacharinsak C. & Felt S.A. (2014) Antinociceptive Effects of Sustained-Release Buprenorphine in a Model of Incisional Pain in Rats (*Rattus norvegicus*). *Journal of the American Association for Laboratory Animal Science* **53**, 193–197.

Chun R., Knapp D.W., Widmer W.R., DeNicola D.B., Glickman N.W., Kuczek T. *et al.* (1997) Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. *Journal of Veterinary Internal Medicine* **11**, 279–283.

Chun R., Garret L.D. & Vail D.M. (2007) *Cancer chemotherapy*. In: *Small Animal Clinical Oncology*. 4th edn, 163–192. (eds S.J. Withrow & D.M. Vail), MO Saunders Elsevier: St. Louis.

Dernell W.S., Withrow S.J., Straw R.C., Powers B.E., Drekke J.H. & Lafferty M. (1997) Intracavitary treatment of soft tissue sarcomas in dogs using cisplatin in a biodegradable polymer. *Anticancer Research* **17**(6D), 4499–4505.

Dunn R.L., Yewey G.L., Fujita S.M., Josephs K.R., Whitman S.L., Southard G.L. *et al.* (1996) Sustained release of cisplatin in dogs from an injectable implant delivery system. *Journal of Bioactive and Compatible Polymers* **11**, 286–300.

Elferink F., Van der Vijgh W.J.F., Klein I. *et al.* (1987) Pharmacokinetics of Carboplatin after IV administration. *Cancer Treatment Reports* **71**, 1231–1237.

Frazier D.L. & Price G.S. (1998) Use of body surface area (BSA)-Based Dosages to calculate chemotherapeutic drug dose in dogs: II. limitations imposed by pharmacokinetic factors. *Journal of Veterinary Internal Medicine* **12**, 272–278.

Gaver R.C., George A.M., Duncan G.F., Morris D.A., Deeb G., Faulker H.C. & Farmen R.H. (1988) The disposition of Carboplatin in the beagle dog. *Cancer Chemotherapy and Pharmacology* **21**, 197–202.

Gavini E., Manunta L., Giua S., Achenza G. & Giunchedi P. (2005) Spray-dried poly (D, L-Lactide) microspheres containing carboplatin for veterinary use: in vitro and In Vivo studies. *AAPS PharmSciTech* **6**, E108–E114.

Hahn K.A., McEntee M.F., Daniel G.B., Legendre A.M., Nolan M.L. (1997) Hematologic and systemic toxicosis associated with carboplatin administration in cats. *American Journal of Veterinary Research* **58**, 677–679.

ICH Q2 (R1) (2005). Validation of Analytical Procedures: Text and Methodology.

Kisseberth W.C., Vail D.M., Yaissle J., Jeglum K.A., Couto C.G., Ward H. *et al.* (2008) Phase I clinical evaluation of Carboplatin in tumor-bearing cats: a veterinary cooperative oncology group study. *Journal of Veterinary Internal Medicine* **22**, 83–88.

Kitchell B.K., Orenberg E.K., Brown D.M., Hutson D.M., Ray K., Woods L. & Luck E. (1995) Intralesional sustained-release chemotherapy with therapeutic implants for treatment of sun-induced squamous cell carcinoma. *European Journal of Cancer* **31A**, 2093–2098.

Lana S.E., Dernell W.S., Larue S.M., Lafferty M.J., Douple E.B., Brekke J.H. & Withrow S.J. (1997) Slow release cisplatin combined with radiation for the treatment of canine nasal tumors. *Veterinary Radiology and Ultrasound* **38**, 474–478.

Manunta M.L., Gavini E., Chessa G., Passino E.S., Careddu G.M., Giua S. *et al.* (2005) Carboplatin sustained delivery system using injectable microspheres. *Journal of Veterinary Medicine A* **52**, 416–422.

Nunamaker E.A., Halliday L.C., Moody D.E., Fang W.B., Lindeblad M. & Fortman J.D. (2013) Pharmacokinetics of 2 formulations of buprenorphine in macaques (*Macaca mulatta* and *Macaca fascicularis*). *Journal of the American Association for Laboratory Animal Science* **52**, 1–9.

Ogilvie G.K., Richardson R.C., Curtis C.R. *et al.* (1989) Acute and short-term toxicoses associated with the administration of doxorubicin to dogs with malignant tumors. *Journal of the American Veterinary Medical Association* **195**, 1584–1587.

Page R.L., McEntee M.C., George S.L., Williams P.L., Heidner G.L., Novotney C.A. *et al.* (1993) Pharmacokinetic and Phase I evaluation of carboplatin in dogs. *Journal of Veterinary Internal Medicine* **7**, 235–240.

Phillips B. (1999) Severe, prolonged bone marrow hypoplasia secondary to the use of Carboplatin in an azotemic dog. *Journal of the American Veterinary Medical Association* **215**, 1250–1256.

Price G.S. & Frazier D.L. (1998) Use of body surface area (BSA)-based dosages to calculate chemotherapeutic drug dose in dogs: I. potential Problems with current BSA Formulae. *Journal of Veterinary Internal Medicine* **12**, 267–271.

Rassnick K.M., Ruslander D.M., Cotter S.M., Al-Sarraf R., Bruyette D.S., Gamblin R.M. *et al.* (2001) Use of carboplatin for treatment of dogs with malignant melanoma: 27 cases (1998-2000). *Journal of the American Veterinary Medical Association* **218**, 1444–1448.

Reed E. (2006) Cisplatin, Carboplatin, and oxaliplatin. In: *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 4th edn, 332–343. (eds B.A. Chabner & D.L.

Long), PA Lippincott Williams and Wilkins: Philadelphia.

Theon A.P., VanVechten M.K. & Madewell B.R. (1996) Intratumoral administration of Carboplatin for treatment of squamous cell carcinomas of the nasal plan in cats. *American Journal of Veterinary Research* **57**, 205–210.

Veterinary Cooperative Oncology Group (2010) Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Veterinary and Comparative Oncology* **8**, 28–37. doi:10.1111/j.1476-5829.2009.00200.x.

Withrow S.J., Straw R.C., Brekke J.H., Powers B.E., Cooper M.F., Ogilvie G.K. *et al.* (1995) Slow release adjuvant cisplatin for treatment of metastatic canine osteosarcoma. *European Journal of Experimental Musculoskeletal Research* **4**, 105–110.