


# Delivery vehicles in Veterinary Oncology

Subjects: Oncology & Oncogenics

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## Definition

Nanomedicine is a recent concept in veterinary oncology and provide the possibility of more specific treatment to the patients. In this critical review, we provided the most updated information regarding the use of nanoparticles in veterinary oncology.

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Controlled drug delivery systems can be used to carry several anticancer agents, including classical chemotherapeutic agents such as doxorubicin, paclitaxel or cisplatin, and are also used for the encapsulation of tyrosine kinase inhibitors and monoclonal antibodies. Usually, the controlled systems are used to decrease drug toxicity, increase local drug concentration or target specific organs or systems. In dogs, liposomal doxorubicin is the most known controlled drug delivery vehicle in veterinary medicine. However, several antitumor drugs can be encapsulated within these systems. Since the delivery vehicles are a relatively new topic in veterinary oncology, this review aims to discuss the current knowledge regarding the controlled drug delivery vehicles and discuss the current challenges and future direction of its use in veterinary oncology.

## 1. Introduction

In the past years, veterinary medicine has been experiencing an increased life expectancy associated with the appearance of several aging-related diseases in pets . Among these diseases, cancer is one of the most prevalent in older dogs <sup>[1]</sup>. The treatment options in veterinary oncology include surgical procedure<sup>[2]</sup>, radiation therapy<sup>[3]</sup>, conventional chemotherapy <sup>[4]</sup>, target therapies <sup>[5]</sup>, electrochemotherapy <sup>[6]</sup> or a combination of these modalities. Although all these therapies have been used in veterinary oncology, we still have poor prognosis when compared with human patients. For this reason, new antitumor therapies are required. Different from humans, cytoreductive chemotherapy is poorly explored for solid tumors in veterinary oncology and tumors as prostatic carcinomas <sup>[7]</sup>, soft tissue sarcoma <sup>[8]</sup>, osteosarcomas <sup>[9]</sup>, hemangiosarcomas <sup>[10]</sup> and mammary gland tumors show poor antitumor response. While conventional chemotherapy has been used in veterinary oncology, some drawbacks of chemotherapy are low therapeutic indices, lack of targets predicting antitumor response, development of drug resistance and low specificity for neoplastic cells.

Performing a critical review of the manuscripts published on PubMed about drug delivery systems in dogs, we identified 2338 publications and most of them, were performed in healthy dogs to evaluated pharmacological properties. Therefore, the current knowledge on drug delivery system in veterinary medicine is focused on the understanding of drug pharmacokinetics and pharmacodynamics, mainly focused on the human health <sup>[11][12][13][14][15]</sup>. Regarding the canine tumors, a high number of articles were on brain tumors <sup>[16][17][18][19][20]</sup>. The use of dogs as models for human brain tumors has been increasing in the last years and these studies usually use controlled drug delivered vehicles in the experimental approach <sup>[16][17][18][19][20]</sup>. Although these studies have the human health as a primary focus, positive antitumor response can benefit dogs and humans. Different studies have used different drug delivered vehicles, including gold particles, liposomes and polymer-based nanoparticles <sup>[16][17][18][19][20][21]</sup>.

There are a high number of studies evaluating drug delivery vehicles in healthy dogs, aiming to increase drug concentration in specific organs <sup>[22]</sup>, drug bioavailability or decrease drug toxicity. Although a high number of studies have investigated pharmacokinetics of different drug delivery vehicles in healthy dogs, a limited number of studies have investigated drugs with anticancer properties in healthy dogs <sup>[23]</sup>. More intriguing, the translation rate of the studies performed in healthy dogs to dogs with cancer is very low. Most likely, because these studies in its majority aim to stablish drug pharmacokinetics with focus on human diseases . Among the studies aiming to decrease drug toxicity through drug encapsulation, cisplatin , paclitaxel and doxorubicin <sup>[24]</sup> were the most studied.

## 2. Paclitaxel

Paclitaxel is widely used in human medicine for treating different cancer subtypes, including metastatic breast cancer in the lungs [25][26]. Paclitaxel is an insoluble drug and should be combined with dehydrated alcohol and polyoxyethylated castor oil [27]. Unfortunately, this combination administered intravenously have proved to induce severe and acute hypersensitivity in dogs and cats [28]. Due to its high hypersensitivity reaction during intravenous administration, Silva et al. [28] evaluated the paclitaxel subcutaneous administration expecting to find a lower rate of side effects. The results showed that even using subcutaneous administration, dogs presented several side effects and a low number of patients received more than one paclitaxel injection. Therefore, authors were not able to establish maximum tolerated dosage and no further studies have used this protocol.

Since one of the side effects of paclitaxel is associated to the hypersensitivity induced by the drug adjuvant, paclitaxel encapsulation in different controlled drug delivery vehicles were previously tested [29][30][31]. Axiak et al. evaluated the safety of paclitaxel nanoparticles (CTI 52010) administration in healthy dogs. These authors showed that paclitaxel nanoparticles (CTI 52010), with a starting dosage of 80 mg/m<sup>2</sup>, was well tolerated after intravenous administration and presented liver, kidney and spleen toxicity (evaluated by histopathology). On the other hand, Zhao et al. [30] evaluated paclitaxel liposomes for a lung target delivered system. Their liposomes were composed of Tween-80/HSPC/cholesterol (0.03:3.84:3.84, mol/mol), containing paclitaxel and lipids (1:40, mol/mol) [30]. These authors evaluated the pharmacokinetics of their preparation in 25 healthy dogs and demonstrated high lung concentration of the paclitaxel liposomes [30]. However, authors did not describe side effects of this administration.

Based on preliminary studies on paclitaxel nanoparticles (CTI 52010) [29], Selting et al. [29] evaluated the paclitaxel nanoparticles (CTI 52010) in tumor bearing dogs. In their study, paclitaxel nanoparticles (CTI 52010) was used in an increasing dosage ranging to 80 mg/m<sup>2</sup> up to 136 mg/m<sup>2</sup>. Fifteen dogs with different tumor subtypes were included and the maximum tolerated dosage could not be determined due the highly variable toxicity among all fifteen dogs [29]. Although it presents some preliminary results, the paclitaxel nanoparticles (CTI 52010) pharmacokinetics was similar in both health (N = 3) and tumor-bearing dogs (N = 15) and this formulation did not induce hypersensitivity. Thus, could be a promising treatment option.

## 3. Doxorubicin

Doxorubicin is an anthracycline antitumor drug originated as a product from *Streptomyces* classified as a chemotherapeutic from the antibiotic class [32]. It is widely used in veterinary medicine for dogs with lymphoma [33], osteosarcoma [34], hemangiosarcoma [35] and mammary gland tumors. However, in dogs [36] and in cats, relevant clinical cardiotoxicity can be highly nephrotoxic [37]. Therefore, new strategies to decrease doxorubicin toxicity has been studied. In this scenario, doxorubicin liposomal encapsulation has been providing promising results [38][39][40]. Using domestic pigs as an experimental model to evaluate the potential of liposomal doxorubicin to induce cardiotoxicity, it was demonstrated a cardiotoxicity attenuation via induction of interferon-related DNA damage resistance [39]. Since the first description of liposomal doxorubicin, several manuscripts were published showing its efficacy in the clinical practice [41][42][43][44][45][46][47][48]. In a previous randomized controlled study evaluating both efficacy and toxicity of encapsulated doxorubicin into pegylated liposome compared to free doxorubicin, there was no statistical difference of overall survival in patients treated with free doxorubicin versus liposomal doxorubicin [42]. Besides that, in the studied group no patients developed cardiotoxicity (even treated with free doxorubicin) [42]. In their study, two dogs treated with liposomal doxorubicin experienced desquamating dermatitis like palmar-plantar erythrodysesthesia and other three presented anaphylactic reactions [42].

After the first studies, liposome-encapsulated doxorubicin has proved to decrease toxicity; however, the clinical efficacy has showed no improvement or only a modest improvement [41][42][43][44][45][46][47][48]. Thus, increased the search for different approaches aiming to increase antitumor response of liposome encapsulated chemotherapy [45]. Hauck et al. [45] evaluated the safety of a low temperature sensitive liposome-encapsulated doxorubicin related with local hyperthermia in dogs with sarcomas or carcinomas. The protocol was well tolerated with acceptable side effects and with favorable antitumor response [45]. Recently, Bredlau et al. evaluated the pharmacokinetics of temperature sensitive liposomes

containing doxorubicin associated with hyperthermia across the canine blood–brain barrier. Their protocol was effective and showed high concentration temperature sensitive liposomes in the central nervous system and the normal tissue presented a very low toxicity. Therefore, this therapy could be promising treating patients with primary brain tumors.

## 4. Cisplatin

Cisplatin is a well-known platinum-based anti-cancer chemotherapy drug used to treat different cancer subtypes<sup>[49]</sup>. Usually show high nephrotoxicity and should be administrated with a diuresis protocol<sup>[49]</sup>. However, a newer platin-derived drug was developed with similar mechanism of action and lower nephrotoxicity<sup>[50]</sup>. Thus, since carboplatin is less toxic than cisplatin and do not need a diuretic protocol, it is a Food and Drug Administration (FDA) approved treatment<sup>[51]</sup>.

Currently, carboplatin is a widely used chemotherapeutic drug, including in the treatment of ovarian, bladder, breast and esophageal cancers<sup>[50]</sup>. When compared to antitumor effects of carboplatin and cisplatin, for some tumor subtypes, cisplatin still shows a better antitumor response than carboplatin. As a result, new strategies for the cisplatin safety use was required<sup>[52]</sup>. Aiming to reduce cisplatin toxicity and increase the drug concentration, cisplatin encapsulation in a liposomal formulation (SPI-77) was previously evaluated<sup>[53]</sup>. The cisplatin liposomal encapsulation allows delivered drug concentration five times more the maximum tolerated dosage when compared to free cisplatin [14,53]. The same research group published the evaluation of SPI-77 cisplatin formulation in healthy dogs [14] and dogs with osteosarcoma [53]. First, this research group evaluated SPI-77 formulation in liposomes containing a pegylated lipid [N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium salt, MPEG-DSPE] in osteosarcoma-affected dogs<sup>[53]</sup>. In their previous study, dogs were treated with SPI-77 formulation containing cisplatin (STEALTH) versus dogs treated with maximum tolerated dosage of carboplatin and they demonstrated no increased toxicity of STEALTH formulation and identified five times higher concentration of drug delivered when compared to free cisplatin. However, their study did not show the difference in overall survival between both treatments<sup>[53]</sup>.

Then, this research group published a manuscript evaluating the efficacy of the liposome encapsulate cisplatin in healthy dogs [14]. The liposome formulation was composed by dipalmitoyl phosphatidyl glycerol, soy phosphatidyl choline, cholesterol, and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine. Four different dosages were tested, including 70, 100, 125, and 150 mg/m<sup>2</sup> in a small group of dogs (N = 4). As expected, the side effects were more frequently in the group treated with higher dosage; however, being acceptable. Thus, authors concluded that the dosage of 150 mg/m<sup>2</sup> can be used without association of hydration protocols<sup>[53]</sup>. However, no further studies evaluated this formulation in tumor-bearing dogs.

Based on the systemic toxicity using free-cisplatin, Venable et al.<sup>[54]</sup> used a natural polysaccharide (Hyaluronan) nanocarrier to conjugate with cisplatin and treat dogs with soft tissue sarcomas. After hyaluronan metabolization, the lymphatic system is responsible for its metabolites elimination via lysosomal and endocytosis degradation [54]. Thus, can be promising in intratumoral formulations. These authors tested their hyaluronan-cisplatin nanoconjugate intratumorally in five client-owned dogs and found no local reaction related to drug administration. Besides that, authors found a higher concentration of cisplatin (1000 ×) intratumorally compared to serum concentrations. Since it was the first manuscript using this formulation in dogs with soft tissue sarcomas, they did not focus on antitumor response. Therefore, in 2016 a phase I/II clinical trial in dogs with spontaneous cancers treated with Hyaluronan-Cisplatin Nanoconjugate was performed<sup>[52]</sup>. In this clinical trial, 16 dogs with different tumors subtyped were used, including anal sac carcinoma, oral squamous cell carcinoma, oral melanoma, nasal carcinoma and digital squamous cell carcinoma. A complete response was observed in three dogs (3/16), one experienced partial response (1/16) and other one stable disease (1/16). Thus, the formulation failed in show antitumor response in 69% of the patients (11/16). Interestingly, three patients with complete response had carcinomas from head and neck (oral or nasal carcinomas). Consequently, this formulation could be promising for carcinomas in this location. However, a new clinical trial should be performed to clarify if this formulation can benefit dogs with head and neck carcinomas. Overall, the current information does not support the use of Hyaluronan-Cisplatin Nanoconjugate in tumor-bearing dogs.

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## Keywords

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