Delivery vehicles in Veterinary Oncology

Subjects: Oncology

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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.

Keywords: veterinary medicine ; veterinary oncology ; nanomedicine ; nanoparticles

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 [1]. The treatment options in veterinary oncology include surgical procedure [2], radiation therapy [3], conventional chemotherapy [4], target therapies [5], electrochemotherapy [6] 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 [7], soft tissue sarcoma [8], osteosarcomas [9], hemangiosarcomas [10] 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 [11][12][13][14][15]. Regarding the canine tumors, a high number of articles were on brain tumors [16][17][18][19][20]. 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 [16][17][18][19][20]. 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 [16][17][18][19][20][21].

There are a high number of studies evaluating drug delivery vehicles in healthy dogs, aiming to increase drug concentration in specific organs [22], 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 [23]. 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 [24] were the most studied.

2. Paclitaxel

Paclitaxel it 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 administrated 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^2, 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 raging to 80 mg/m^2 up to 136 mg/m^2. 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 [49]. Usually show high nephrotoxicity and should be administrated with a diuresis protocol [49]. However, a newer platin-derived drug was developed with similar mechanism of action and lower nephrotoxicity [50]. 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 [51].

Currently, carboplatin is a widely used chemotherapeutic drug, including in the treatment of ovarian, bladder, breast and esophageal cancers [50]. 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 [52]. Aiming to reduce cisplatin toxicity and increase the drug concentration, cisplatin encapsulation in a liposomal formulation (SPI-77) was previously evaluated [53]. 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 [53]. 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 [53].

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^2 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^2 can be used without association of hydration protocols [53]. However, no further studies evaluated this formulation in tumor-bearing dogs.

Based on the systemic toxicity using free-cisplatin, Venable et al. [54] 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 [52]. 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.

References

1. Dos Anjos, D.S.; Vital, A.F.; Lainetti, P.F.; Leis-Filho, A.F.; Dalmolin, F.; Elias, F.; Calazans, S.G.; Fonseca-Alves, C.E. Deregulation of VEGFR-2 and PDGFR Expression and Microvascular Density in a Triple-Negative Model of Canine Malignant Mammary Tumors with Lymph Node or Lung Metastasis. Vet. Sci. 2019, 6, E3, doi:10.3390/vetsci6010003.
2. Boston, S.; Henderson, R.A., Jr. Role of surgery in multimodal cancer therapy for small animals. Vet. Clin. Small Anim. Pract. 2014, 44, 855–870, doi:10.1016/j.cvsm.2014.05.008.
3. Meier, V.S.; Beatrice, L.; Turek, M.; Poirier, V.J.; Cancedda, S.; Stiborova, K.; Körner, M.; Marconato, L.; Weyland, M.S.; Rohrer Bley, C. Outcome and failure patterns of localized sinonasal lymphoma in cats treated with first-line single-modality radiation therapy: A retrospective study. Vet. Comp. Oncol. 2019, 17, 528–536, doi:10.1111/vco.12517.

4. Kent, M.S. Cats and chemotherapy: Treat as ‘small dogs’ at your peril. J. Feline Med. Surg. 2013, 15, 419–424, doi:10.1177/1098612X13483240.
5. Prado, M.C.M.; Macedo, S.A.L.; Guiraldelli, G.G.; de Faria Lainetti, P.; Leis-Filho, A.F.; Kobayashi, P.E.; Laufer-Amorim, R.; Fonseca-Alves, C.E. Investigation of the Prognostic Significance of Vasculogenic Mimicry and Its Inhibition by Sorafenib in Canine Mammary Gland Tumors. Front. Oncol. 2019, 9, 1445, doi:10.3389/fonc.2019.01445.
6. Dos Anjos, D.S.; Bueno, C.; Magalhães, L.F.; Magalhães, G.M.; Mattos-Junior, E.; Pinto, M.M.R.; De Nardi, A.B.; Brunner, C.H.M.; Leis-Filho, A.F.; Calazans, S.G.; et al. Electrochemotherapy induces tumor regression and decreases the proliferative index in canine cutaneous squamous cell carcinoma. Sci. Rep. 2019, 9, 15819, doi:10.1038/s41598-019-52461-6.
7. Fonseca-Alves, C.E.; Kobayashi, P.E.; Leis-Filho, A.F.; Lainetti, P.F.; Grieco, V.; Kuasne, H.; Rogatto, S.R.; Laufer-Amorim, R. E-Cadherin Downregulation is Mediated by Promoter Methylation in Canine Prostate Cancer. Front. Genet. 2019, 10, 1242, doi:10.3389/fgene.2019.01242.
8. Hohenhaus, A.E.; Kelsey, J.L.; Haddad, J.; Barber, L.; Palmisano, M.; Farrelly, J.; Soucy, A. Canine Cutaneous and Subcutaneous Soft Tissue Sarcoma: An Evidence-Based Review of Case Management. J. Am. Anim. Hosp. Assoc. 2016, 52, 77–89, doi:10.5326/JAAHA-MS-6305.
9. Turner, H.; Séguin, B.; Worley, D.R.; Ehrhart, N.P.; Lafferty, M.H.; Withrow, S.J.; Selmic, L.E. Prognosis for dogs with stage III osteosarcoma following treatment with amputation and chemotherapy with and without metastasectomy. J. Am. Vet. Med. Assoc. 2017, 251, 1293–1305, doi:10.2460/javma.251.11.1293.
10. Wendelburg, K.M.; Price, L.L.; Burgess, K.E.; Lyons, J.A.; Lew, F.H.; Berg, J. Survival time of dogs with splenic hemangiosarcoma treated by splenectomy with or without adjuvant chemotherapy: 208 cases (2001–2012). J. Am. Vet. Med. Assoc. 2015, 247, 393–403, doi:10.2460/javma.247.4.393.
11. Axiak, S.M.; Selting, K.A.; Decedue, C.J.; Henry, C.J.; Tate, D.; Howell, J.; Bilof, K.J.; Kim, D.Y. Phase I dose escalation safety study of nanoparticulate paclitaxel (CTI 52010) in normal dogs. Int. J. Nanomed. 2011, 6, 2205–2212, doi:10.2147/IJN.S24823.
12. Bredlau, A.L.; Motamarry, A.; Chen, C.; McCrackin, M.A.; Helke, K.; Armeson, K.E.; Bynum, K.; Broome, A.M.; Haemmerich, D. Localized delivery of therapeutic doxorubicin dose across the canine blood-brain barrier with hyperthermia and temperature sensitive liposomes. Drug Deliv. 2018, 25, 973–984, doi:10.1080/10717544.2018.1461280.
13. Kesisoglou, F.; Wang, M.; Galipeau, K.; Harmon, P.; Okoh, G.; Xu, W. Effect of Amorphous Nanoparticle Size on Bioavailability of Anacetrapib in Dogs. J. Pharm. Sci. 2019, 108, 2917–2925, doi:10.1016/j.xphs.2019.04.006.
14. Marr, A.K.; Kurzman, I.D.; Vail, D.M. Preclinical evaluation of a liposome-encapsulated formulation of cisplatin in clinically normal dogs. Am. J. Vet. Res. 2004, 65, 1474–1478.
15. Prélaud, A.R.; Fuchs, S.; Weber, K.; Winter, G.; Coester, C.; Mueller, R.S. In vitro effects of CpG oligodeoxynucleotides delivered by gelatin nanoparticles on canine peripheral blood mononuclear cells of atopic and healthy dogs—a pilot study. Vet. Dermatol. 2013, 24, 494-e117, doi:10.1111/vde.12056.
16. Arami, H.; Patel, C.B.; Madsen, S.J.; Dickinson, P.J.; Davis, R.M.; Zeng, Y.; Sturges, B.K.; Woolard, K.D.; Habte, F.G.; Akin, D.; et al. Nanomedicine for Spontaneous Brain Tumors: A Companion Clinical Trial. ACS Nano 2019, 13, 2858–2869, doi:10.1021/acsnano.8b04406.
17. Lee, J.; Cho, H.R.; Cha, G.D.; Seo, H.; Lee, S.; Park, C.K.; Kim, J.W.; Qiao, S.; Wang, L.; Kang, D.; et al. Flexible, sticky, and biodegradable wireless device for drug delivery to brain tumors. Nat. Commun. 2019, 10, 5205, doi:10.1038/s41467-019-13198-y.
18. Young, J.S.; Bernal, G.; Polster, S.P.; Nunez, L.; Larsen, G.F.; Mansour, N.; Podell, M.; Yamini, B. Convection-Enhanced Delivery of Polymeric Nanoparticles Encapsulating Chemotherapy in Canines with Spontaneous Supratentorial Tumors. World Neurosurg. 2018, 117, e698–e704, doi:10.1016/j.wneu.2018.06.114.
19. Freeman, A.C.; Platt, S.R.; Holmes, S.; Kent, M.; Robinson, K.; Howerth, E.; Eagleson, J.; Bouras, A.; Kaluzova, M.; Hadjipanayis, C.G. Convection-enhanced delivery of cetuximab conjugated iron-oxide nanoparticles for treatment of spontaneous canine intracranial gliomas. J. Neurooncol. 2018, 137, 653–663, doi:10.1007/s11060-018-2764-1.
20. Rossmeisl, J. Maximizing Local Access to Therapeutic Deliveries in Glioblastoma. Part V: Clinically Relevant Model for Testing New Therapeutic Approaches. In Glioblastoma [Internet]; De Vleeschouwer, S., Ed.; Codon Publications: Brisbane, Australia, 2017; Available online: http://www.ncbi.nlm.nih.gov/books/NBK470000 (accessed on 20 April, 2020).
21. Park, S.Y.; Kang, Z.; Thapa, P.; Jin, Y.S.; Park, J.W.; Lim, H.J.; Lee, J.Y.; Lee, S.W.; Seo, M.H.; Kim, M.S.; et al. Development of sorafenib loaded nanoparticles to improve oral bioavailability using a quality by design approach. Int. J. Pharm. 2019, 566, 229–238, doi:10.1016/j.ijpharm.2019.05.064.

22. Grabtchak, S.; Montgomery, L.G.; Whelan, W.M. Feasibility of interstitial near-infrared radiance spectroscopy platform for ex vivo canine prostate studies: Optical properties extraction, hemoglobin and water concentration, and gold nanoparticles detection. J. Biomed. Opt. 2014, 19, 057003, doi:10.1117/1.JBO.19.5.057003.

23. Feldhaeusser, B.; Platt, S.R.; Marrache, S.; Kolishetti, N.; Pathak, R.K.; Montgomery, D.J.; Reno, L.R.; Howerth, E.; Dhar, S. Evaluation of nanoparticle delivered cisplatin in beagles. Nanoscale 2015, 7, 13822–13830, doi:10.1039/c5nr03447g.

24. Xie, Y.; Shao, N.; Jin, Y.; Zhang, L.; Jiang, H.; Xiong, N.; Su, F.; Xu, H. Determination of non-liposomal and liposomal doxorubicin in plasma by LC-MS/MS coupled with an effective solid phase extraction: In comparison with ultrafiltration technique and application to a pharmacokinetic study. J. Chromatogr. B 2018, 1072, 149–160, doi:10.1016/j.jchromb.2017.11.020.

25. Aktas, B.Y.; Taban, H.; Aksoy, S. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N. Engl. J. Med. 2019, 380, 985–986, doi:10.1056/NEJMc1900150.

26. Wardhani, B.W.; Puteri, M.U.; Watanabe, Y.; Louisa, M.; Setiabudy, R.; Kato, M. TGF-β-Induced TMEPAI Attenuates the Response of Triple-Negative Breast Cancer Cells to Doxorubicin and Paclitaxel. J. Exp. Pharmacol. 2020, 12, 17–26, doi:10.2147/JEP.S235233.

27. Poirier, V.J.; Hershey, A.E.; Burgess, K.E.; Phillips, B.; Turek, M.M.; Forrest, L.J.; Beaver, L.; Vail, D.M. Efficacy and toxicity of paclitaxel (Taxol) for the treatment of canine malignant tumors. J. Vet. Intern. Med. 2004, 18, 219–222.

28. Silva, D.M.; Franciosi, A.I.; Pezzini, P.C.; Guérios, S.D. Subcutaneous administration of paclitaxel in dogs with cancer: A preliminary study. Can. Vet. J. 2015, 56, 823–830.

29. Selting, K.A.; Bechtel, S.M.; Espinosa, J.; Henry, C.J.; Tate, D.; Bryan, J.N.; Rajewski, L.; Flesner, B.K.; Decedue, C.; Baltezor, M. Evaluation of intravenous and subcutaneous administration of a novel, excipient-free, nanoparticulate formulation of paclitaxel in dogs with spontaneously occurring neoplasia. Vet. Comp. Oncol. 2018, 16, 650–657, doi:10.1111/vco.12435.

30. Zhao, L.; Ye, Y.; Li, J.; Wei, Y.M. Preparation and the in-vivo evaluation of paclitaxel liposomes for lung targeting delivery in dogs. J. Pharm. Pharmacol. 2011, 63, 80–86, doi:10.1111/j.2042-7158.2010.01184.x.

31. Axiak-Bechtel, S.M.; Kumar, S.R.; Dank, K.K.; Clarkson, N.A.; Selting, K.A.; Bryan, J.N.; Rosol, T.J.; Espinosa, J.; Decedue, C.J. Nanoparticulate paclitaxel demonstrates antitumor activity in PC3 and Ace-1 aggressive prostate cancer cell lines. Invest. New Drugs 2013, 31, 1609–1615, doi:10.1007/s10637-013-0006-0.

32. Young, R.C.; Ozols, R.F.; Myers, C.E. The anthracycline antineoplastic drugs. N. Engl. J. Med. 1981, 305, 139–153.

33. Ogilvie, G.K.; Fettman, M.J.; Mallinckrodt, C.H.; Walton, J.A.; Hansen, R.A.; Davenport, D.J.; Gross, K.L.; Richardson, K.L.; Rogers, Q.; Hand, M.S. Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma: A double-blind, randomized placebo-controlled study. Cancer 2000, 88, 1916–1928.

34. Mauldin, G.N.; Matus, R.E.; Withrow, S.J.; Patnaik, A.K. Canine osteosarcoma. Treatment by amputation versus amputation and adjuvant chemotherapy using doxorubicin and cisplatin. J. Vet. Intern. Med. 1988, 2, 177–180.

35. Sorenmo, K.U.; Jeglum, K.A.; Helfand, S.C. Chemotherapy of canine hemangiosarcoma with doxorubicin and cyclophosphamide. J. Vet. Intern. Med. 1993, 7, 370–376.

36. Withers, S.S.; Kass, P.H.; Rodriguez, C.O., Jr.; Skorupski, K.A.; O'Brien, D.; Guerrero, T.A.; Sein, K.D.; Rebhun, R.B. Fasting reduces the incidence of delayed-type vomiting associated with doxorubicin treatment in dogs with lymphoma. Transl. Oncol. 2014, 7, 377–383.

37. O'Keefe, D.A.; Sisson, D.D.; Gelberg, H.B.; Schaeffer, D.J.; Krawiec, D.R. Systemic toxicity associated with doxorubicin administration in cats. J. Vet. Intern. Med. 1993, 7, 309–317.

38. Vail, D.M.; Kravis, L.D.; Cooley, A.J.; Chun, R.; MacEwen, E.G. Preclinical trial of doxorubicin entrapped in sterically stabilized liposomes in dogs with spontaneously arising malignant tumors. Cancer Chemother. Pharmacol. 1997, 39, 410–416.

39. Gyöngyösi, M.; Lukovic, D.; Zlabinger, K.; Spannbauer, A.; Gugerell, A.; Pavo, N.; Traxler, D.; Pils, D.; Maurer, G.; Jakab, A.; et al. Liposomal doxorubicin attenuates cardiotoxicity via induction of interferon-related DNA damage resistance. Cardiovasc. Res. 2019, 116, cvz192, doi:10.1093/cvr/cvz192.

40. Working, P.K.; Newman, M.S.; Sullivan, T.; Yarrington, J. Reduction of the cardiotoxicity of doxorubicin in rabbits and dogs by encapsulation in long-circulating, pegylated liposomes. J. Pharmacol. Exp. Ther. 1999, 289, 1128–1133.

41. Sorenmo, K.; Samluk, M.; Clifford, C.; Baez, J.; Barrett, J.S.; Poppenga, R.; Overley, B.; Skorupski, K.; Oberthaler, K.; Van Winkle, T.; et al. Clinical and pharmacokinetic characteristics of intracavitary administration of pegylated liposomal encapsulated doxorubicin in dogs with splenic hemangiosarcoma. J. Vet. Intern. Med. 2007, 21, 1347–1354.

42. Teske, E.; Rutteman, G.R.; Kirpenstein, J.; Hirschberger, J. A randomized controlled study into the efficacy and toxicity of pegylated liposome encapsulated doxorubicin as an adjuvant therapy in dogs with splenic haemangiosarcoma. Vet. Comp. Oncol. 2011, 9, 283–289, doi:10.1111/j.1476-5829.2011.00266.x.
43. Wójcik, M.; Lewandowski, W.; Król, M.; Pawłowski, K.; Mieczkowski, J.; Lechowski, R.; Zabielska, K. Enhancing anti-tumor efficacy of Doxorubicin by non-covalent conjugation to gold nanoparticles—in vitro studies on feline fibrosarcoma cell lines. PLoS ONE 2015, 10, e0124955, doi:10.1371/journal.pone.0124955. eCollection
44. Yin, Q.; Tang, L.; Cai, K.; Tong, R.; Sternberg, R.; Yang, X.; Dobrucki, L.W.; Borst, L.B.; Kamstock, D.; Song, Z.; et al. Pamidronate functionalized nanoconjugates for targeted therapy of focal skeletal malignant osteolysis. Proc. Natl. Acad. Sci. USA 2016, 113, E4601–E4609, doi:10.1073/pnas.1603316113.
45. Hauck, M.L.; LaRue, S.M.; Petros, W.P.; Poulson, J.M.; Yu, D.; Spasojevic, I.; Pruitt, A.F.; Klein, A.; Case, B.; Thrall, D.E.; et al. Phase I trial of doxorubicin-containing low temperature sensitive liposomes in spontaneous canine tumors. Clin. Cancer Res. 2006, 12, 4004–4010.
46. Kisseberth, W.C.; MacEwen, E.G.; Helfand, S.C.; Vail, D.M.; London, C.L.; Keller, E. Response to liposome-encapsulated doxorubicin (TLC D-99) in a dog with myeloma. J. Vet. Intern. Med. 1995, 9, 425–428.
47. Kleiter, M.; Tichy, A.; Willmann, M.; Pagitz, M.; Wolfesberger, B. Concomitant liposomal doxorubicin and daily palliative radiotherapy in advanced feline soft tissue sarcomas. Vet. Radiol. Ultrasound 2010, 51, 349–355.
48. Griffin, L.; Frank, C.B.; Seguin, B. Pilot study to evaluate the efficacy of lymphotropic nanoparticle enhanced MRI for diagnosis of metastatic disease in canine head and neck tumours. Vet. Comp. Oncol. 2019, doi:10.1111/vco.12527.
49. Dasari, S.; Tchounwou, P.B. Cisplatin in cancer therapy: Molecular mechanisms of action. Eur. J. Pharmacol. 2014, 740, 364–378, doi:10.1016/j.ejphar.2014.07.025.
50. Sousa, G.F.; Wlodarczyk, S.R.; Monteiro, G. Carboplatin: Molecular mechanisms of action associated with chemoresistance. Braz. J. Pharm. Sci. 2014, 50, 693–701, doi:10.1590/S1984-82502014000400004.
51. Food and Drug Administration—FDA. PARAPLATIN®. 2004. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20452scs001_paraplatin_lbl.pdf (accessed on 20 April, 2020).
52. Cai, S.; Zhang, T.; Forrest, W.C.; Yang, Q.; Groer, C.; Mohr, E.; Aires, D.J.; Axiak-Bechtel, S.M.; Flesner, B.K.; Henry, C.J.; et al. Phase I-II clinical trial of hyaluronan-cisplatin nanoconjugate in dogs with naturally occurring malignant tumors. Am. J. Vet. Res. 2016, 77, 1005–1016, doi:10.2460/ajvr.77.9.1005.
53. Vail, D.M.; Kurzman, I.D.; Glawe, P.C.; O'Brien, M.G.; Chun, R.; Garrett, L.D.; Obradovich, J.E.; Fred, R.M., 3rd; Khanna, C.; Colbern, G.T.; et al. STEALTH liposome-encapsulated cisplatin (SPI-77) versus carboplatin as adjuvant therapy for spontaneously arising osteosarcoma (OSA) in the dog: A randomized multicenter clinical trial. Cancer Chemother. Pharmacol. 2002, 50, 131–136.
54. Venable, R.O.; Worley, D.R.; Gustafson, D.L.; Hansen, R.J.; Ehrhart, E.J., 3rd; Cai, S.; Cohen, M.S.; Forrest, M.L. Effects of intratumoral administration of a hyaluronan-cisplatin nanoconjugate to five dogs with soft tissue sarcomas. Am. J. Vet. Res. 2012, 73, 1969–1976, doi:10.2460/ajvr.73.12.1969.