The Veterinary Journal 205 (2015) 189–197

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Nanomedicine in veterinary oncology

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ARTICLE INFO

Article history:
Accepted 11 February 2015

Keywords:
Nanomedicine
Nanoparticles
Chemotherapy
Drug delivery
Oncology
Veterinary

ABSTRACT

Nanomedicine is an interdisciplinary field that combines medicine, engineering, chemistry, biology and material sciences to improve disease management and can be especially valuable in oncology. Nanoparticle-based agents that possess functions such as tumor targeting, imaging and therapy are currently under intensive investigation. This review introduces the basic concept of nanomedicine and the classification of nanoparticles. Because of their favorable pharmacokinetics, tumor targeting properties, and resulting superior efficacy and toxicity profiles, nanoparticle-based agents can overcome several limitations associated with conventional diagnostic and therapeutic protocols in veterinary oncology.

The two most important tumor targeting mechanisms (passive and active tumor targeting) and their dominating factors (i.e. shape, charge, size and nanoparticle surface display) are discussed. The review summarizes published clinical and preclinical studies that utilize different nanoformulations in veterinary oncology, as well as the application of nanoparticles for cancer diagnosis and imaging. The toxicology of various nanoformulations is also considered. Given the benefits of nanoformulations demonstrated in human medicine, nanoformulated drugs are likely to gain more traction in veterinary oncology.

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Introduction

Nanotechnology is an emerging field that has shown great promise in the development of novel diagnostic, imaging and therapeutic agents for a variety of diseases, including cancer (Davis et al., 2008). It exploits the improved and often novel physical, chemical and biological properties of materials on a nanometer scale. Nanomedicine is defined as the application of nanotechnology to medical diagnosis, therapy and prevention.

Nanoformulations seek to overcome several limitations of conventional drugs, including toxicity, poor water solubility, instability (e.g. small interfering RNA, or siRNA) and pharmacokinetic (PK) properties, and may also contribute to the advancement of personalized medicine and to the customization of healthcare (Eifler and Thaxton, 2011). Taking advantage of versatile payloads, favorable PKs, unique tumor targeting properties with both passive and active mechanisms, and an overall superior efficacy and toxicity profile, these nanoscale 'theranostic' (therapeutic–diagnostic, i.e. combining therapeutic and diagnostic purposes) formulations represent potential breakthroughs for cancer therapy and have created a new field known as 'cancer nanomedicine' (Chow and Ho, 2013).

Companion animals, such as cats and dogs, spontaneously develop various types of cancers, such as oral squamous cell carcinoma (SCC), mammary carcinoma, osteosarcoma (OSA) and transitional cell carcinomas, which closely resemble cancers in humans (Rowell et al., 2011). Consequently, spontaneous cancers in cats and dogs have been proposed as the best animal models for human cancers and have been used in preclinical studies for novel drug development, including nanoformulated drugs or imaging probes (De Vico et al., 2005; Withrow and Wilkins, 2010; Rowell et al., 2011).

This review focuses on nanoformulations that have been reported in preclinical studies using companion animals or in early phase clinical trials in veterinary medicine.

Nanoparticle classification and tumor targeting properties

Composition of nanoparticles

Nanoparticles can be categorized as inorganic or 'solid' (gold, iron oxide, quantum dots and carbon nanotubes), or as organic or 'soft' (liposomes, dendrimers, polymeric micelles, and protein aggregates) (Yu et al., 2012; Bao et al., 2013; Cheng et al., 2014). Each nanoparticle category has distinct advantages and limitations; for instance, quantum dots and iron oxide particles have well known fluorescence imaging capability and magnetic resonance imaging (MRI) contrast properties, respectively, but are limited as drug delivery vehicles (Lovell et al., 2011; Li et al., 2014). Conversely, liposomes and polymeric micelles are used clinically for drug delivery, but offer limited applications as imaging agents.

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http://dx.doi.org/10.1016/j.tvjl.2015.02.015
1090-0233/Published by Elsevier Ltd.

Novel nanomedicine platforms can be developed that synthesize hybrid nanoparticles. Specifically, these synthetic theranostic nanoparticles merge the therapeutic potential of the polymeric soft nanoparticle domains with the diagnostic properties of inorganic solid nanoparticles. Most recently, a few novel organic theranostic nanoplatforms have been touted for their potential applications in optical imaging, MRI, positron emission tomography (PET), chemotherapy, photodynamic therapy (PDT) and photothermal therapy (Lovell et al., 2011; Li et al., 2014).

Factors associated with passive tumor targeting

The tumor vasculature and lymphatic vessels are known to be leaky to macromolecules. Thus, nanoparticles can preferentially accumulate in tumors via enhanced permeability and retention (EPR) effects (Matsumura and Maeda, 1986) (Fig. 1). Size, surface charge and shape dictate the interaction of nanoparticles in living subjects. These nanoparticle-specific properties will affect their PK, biodistribution and diffusivity, and consequently determine their in vivo efficacy and toxicity profiles.

Nanoparticle size affects the rate of nanoparticle intratumoral deposition through the EPR effect and therapeutic efficacy. The optimal nanoparticle size for passive tumor targeting is ~10–100 nm (Davis et al., 2008). Hydrophilic components, such as polyethylene glycol (PEG), have been used to coat the surface of nanoparticles to minimize their interaction with blood proteins and reduce their subsequent sequestration by macrophages (Gref et al., 1994; Zahr et al., 2006; Schipper et al., 2009). Unfortunately, the generation of anti-PEG IgM results in accelerated blood clearance and decreased liposomal drug circulation time (Suzuki et al., 2012; Abu Lila et al., 2013) (Table 1, liposomal topotecan in dogs) with repeated PEGylated liposome administration.

The surface charge (i.e. positive, neutral or negative) and density also need to be optimized to prolong the blood circulation time, minimize non-specific clearance and prevent loss to undesired locations. In addition, the shape of nanoparticles affects their blood circulation, ability to marginate and binding affinity, and therefore the rate of tumor deposition and therapeutic efficacy; for example, rods and hollow cubes enter tumors more readily than discs or spheres (Wang et al., 2013b).

Active cancer targeting strategy

Active targeting is more attractive than passive EPR because of improved efficiency, specific delivery of more therapeutic drugs/probes to target sites and the potential for individualized treatment. As shown in Fig. 1, taking advantage of specific cancer cell surface receptors (e.g. folate, transferrin, asialoglycoprotein, integrins, epidermal growth factor receptors, CD44) and unique tumor microenvironment signaling molecules (e.g. vascular endothelial growth factor, matrix metalloproteinases, $\alpha_v\beta_3$ integrin), a broad variety of ligands (e.g. antibodies, single-chain Fv fragments, peptides, small molecules, aptamers) can be bound to the surface of nanoparticles for cancer-targeting therapy (Zhang et al., 2007; Dhar et al., 2008; McCarron et al., 2008; Lu et al., 2009). Compared to the EPR effect alone, these 'active' targeting methods enhance delivery, allow for deeper tumor penetration, and prolong drug retention within both the blood and the tumor, resulting in superior anti-cancer efficacy, specificity and biodistribution (Fig. 1).

Our laboratory has identified a urinary bladder cancer specific peptide, PLZ4, which specifically recognizes dog and human neoplastic, but not normal or inflamed urothelial cells, fibroblasts or white blood cells. When PLZ4 is displayed on the surface of micelles by the self-assembly of telodendrimers, these 'active bladder cancer targeting micelles' are considered to be theranostic because they can deliver chemotherapeutic drugs (doxorubicin or paclitaxel) and fluorescence dyes to bladder cancer cells (Fig. 2). These micelles enhance the anti-cancer efficacy in a bladder xenograft mouse model (Zhang et al., 2007; Lin et al., 2012).

Nanoparticle-based drug delivery systems for veterinary oncology

Nanoparticles have been used to deliver chemotherapeutic drugs, small molecule inhibitors and cytokines to tumor sites. Different formulations may enhance the therapeutic index, increase the

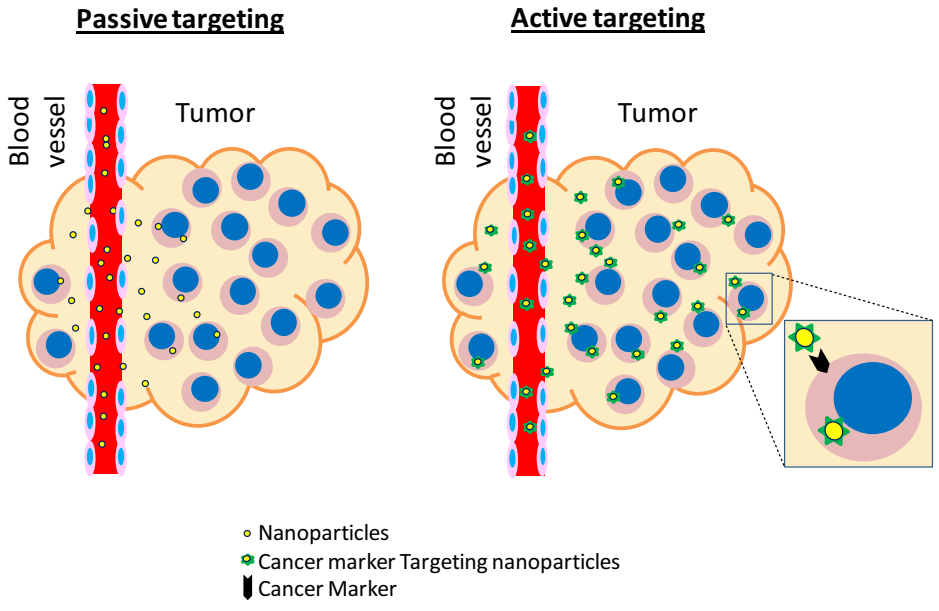

Fig. 1. Passive and active tumor targeting mechanisms of nanoparticles. Blood vessels in tumors are relatively 'leaky' and thus allow nanoparticles to escape the blood circulation and enter tumor tissues. Through surface modification with tumor targeting molecules, nanoparticles are able to further specifically recognize tumor cells after extravasation. Then, through recognition of the unique cancer marker, receptor-mediated endocytosis occurs. In general, active cancer targeting strategy delivers greater amounts of drug and has deeper tumor penetration than conventionally administered chemotherapy or uncoated nanoparticles.