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Enhancing Animal Health: Recent Advances in Liposome-Based Veterinary Therapeutics

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Abstract

Several liposome-based formulations received approval by the U.S. Food and Drug Administration and European Medicines Agency, with many others in clinical trials. Liposomes have several advantages, including improved pharmacokinetic properties of the encapsulated drug, reduced systemic toxicity, extended circulation time, and targeted disposition in tumor sites due to the enhanced permeability and retention mechanism. However, it is worth noting that despite their efficacy in treating various cancers, liposomes still have some potential toxicity and lack specific targeting and disposition.

The focus of this review will be to highlight recent developments in liposome-based therapeutics that are relevant for veterinary medicine. This review will recap recent and ongoing research on liposome-based therapeutics in cancer therapy, vaccine delivery, and pain management in species of veterinary and agricultural relevance.

Introduction

The most clinically useful staging system is the TNM staging, which refers to tumor, node, and metastasis, respectively. This system was developed by the American Joint Committee on Cancer (AJCC) and has since been referred to as the AJCC TNM system [1-5]. The TNM staging system assesses the size of the tumor, the involvement of regional lymph nodes, and any evidence of distant metastasis. Cancer is the second leading cause of death and constitutes a major public health burden worldwide. In the United States, it is estimated that one in three women and one in two men will be diagnosed with cancer in their lifetimes.

The development of resistance to chemotherapy of many cancer types:

Carcinoma – this cancer begins in the skin or in tissues that line or cover internal organs. There are different subtypes, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.

Sarcoma – this cancer begins in the connective or supportive tissues such as bone, cartilage, fat, muscle or blood vessels.

Leukemia – this is cancer of the white blood cells. It starts in the tissues that make blood cells such as the bone marrow.

Lymphoma and myeloma – these cancers begin in the cells of the immune system.

Brain and spinal cord cancers – these are known as central nervous system cancers.

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The mechanisms of resistance to chemotherapy are still not completely understood, but include the activation of cellular survival pathways to inhibit cell death mechanisms, as well as possible epigenetic mechanisms that are yet to be fully elucidated. Liposomes are easily formulated, highly modifiable, and easily administered delivery platforms. They are biodegradable and nontoxic and have long in vivo circulation time. This review focuses on recent and ongoing research that may have relevance for veterinary medicine [8-11].

Liposomes as delivery platforms

Liposomes are round vesicles depicted by a lipids bilayer with an internal aqueous center. The other parts of the structure are phospholipids consolidated with sterols to facilitate film penetrability. Thin-film hydration is the most generally utilized formulation strategy for liposomes, in which lipid parts with or without a drug are broken down in an organic solvent [12]. They can encapsulate both hydrophobic and hydrophilic compounds and can be used for intracellular drug delivery finally; liposomes can be designed for triggered release using external stimuli such as pH, ultrasound, and temperature [13]. Temperature-sensitive liposomes are designed with thermo sensitive polymers that have lower critical solution temperatures attached to their surface. At temperatures below their LCST the polymer chains are stable and hydrated, but at temperatures higher than the LCST .they become dehydrated and disrupt the lipid bilayer, resulting in an immediate release of entrapped contents.

These Nano drug delivery systems are known to enhance the therapeutic indices of the incorporated drugs through a number of ways. These delivery systems protect the entrapped agent from the internal body environment, improve the bioavailability and pharmacokinetics of the drug, and are able to evade immune capture allowing for sustained-release of the drug over time, and lower drug-associated toxicity by improving site-specific delivery [14].

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Liposome-based cancer therapeutics

Modern cancer therapy involves the use of several antineoplastic agents, many of which are chemotherapeutic drugs. These drugs are potent at eliminating cancer cells in vitro but are observed to have significant barriers to in vivo efficacy. These barriers include a lack of selectivity for cancer cells, low bioavailability at tumor sites, larger volumes of distribution, and toxicity to normal tissues. Liposome-encapsulated muramyl tripeptide conjugated with phosphatidylethanolamine was given to dogs as an immunotherapy adjuvant to Doxorubicin chemotherapy and resulted in prolonged disease-free survival in the morbid canines. That is the case with liposome-encapsulated Doxorubicin which demonstrates favourable pharmacokinetic profiles and lower cardio toxicity in human patients as opposed to free Doxorubicin. PEGylated liposomes containing Doxorubicin are available for clinical use in humans, as Doxil. Despite observable increases of drug levels at tumors sites, the clinical outcomes of human patients treated with liposome-encapsulated Doxorubicin have been the same as those treated with free Doxorubicin [15]. The genotypic changes include: mutations, gene amplifications, deletions, and chromosomal rearrangements, transposition of the genetic elements, translocations and microRNA alteration. Genomic instability generates a great level of intercellular genetic heterogeneity in cancer. Epigenetic factors including miRNA, transcriptomic and proteomic heterogeneity may rise due to primary genotypic variations, but can also reflect cell cycle stage, stochastic variations between cells, or hierarchical organization of cells according to the cancer stem cell theory. Finally, it is important to note that recent developments in nanoparticle-based cancer therapeutics are aimed towards nanoparticles with high specificity for certain cells and furthermore certain organelles within a cell. A recent study reported the use of a Doxorubicin-containing liposomes conjugated with a 10 amino acid "tumour metastasis targeting" (TMT) peptide. The TMT liposomes were found to be actively targeted to and endocytosis by metastatic tumour cells in a nude mouse animal model. The active-targeted liposome formulation of Doxorubicin demonstrated effective inhibition of metastatic tumor's in vivo with minimal side effects [16].

Liposome-based analgesia

In contrast with human medicine, where for the most part, patients can self-administer pain medications orally, veterinary pain management requires frequent dosing and rigorous administration protocols. This necessitates frequent handling and higher logistical costs and increases risks of zoonotic infections for animal handlers. To overcome these obstacles, novel drug delivery systems are continually being devised. This formulation has been evaluated in both rabbits and dogs and has been demonstrated to provide extended-release analgesia with no adverse effects. Opioids remain the most widely studied analgesic drugs for liposomal delivery. The ability of liposome-encapsulated oxymorphone and liposome-encapsulated-hydromorphone to prevent hyperalgesia in rat models of induced neuropathic pain has been well documented [17].

Conclusion

As the costs associated with veterinary medicine increase, it will be imperative to channel resources into cost-effective, high-efficiency, and low-risk drug delivery systems. To conclude, it is important to discuss some of the future directions of liposome-based research in veterinary medicine. In addition to curative therapies, liposomes may also be used for dietary supplementation in animals. A study conducted in post pubertal cows demonstrated that an oral administration of liposome-encapsulated α-tocopherol resulted in longer lasting plasma concentrations than other formulations of this essential vitamin. The use of liposomes to improve drug delivery has greatly impacted various biomedical areas. Liposomes have been shown to improve stability and bio distribution of therapeutic agents, overcome limitations to tissue and cellular uptake in target sites in vivo, and reduce systemic toxicity associated with non-encapsulated agents. The combination therapy is the best option for drug resisted type of cancers. In this context, we reviewed different involved mechanisms in drug resistance and finally, we found the epigenetic drugs and synergy or an additive effect between established chemotherapeutic agents in combination with each other might provide a new strategy in drug resistance cancers. The replacement of tumor suppressor miRNA and suppression of oncomiRs can regulate cancerous cells by suppressing their target genes which are involved in cancer development especially cancer drug resistance.

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