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New Drugs

Liposomal nanomedicines in the treatment of prostate cancer

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ABSTRACT

Prostate cancer is the most common cancer type and the second leading cause of death from cancer in males. In most cases, no curative treatment options are available for metastatic castration-resistant prostate cancer as these tumors are highly resistant to chemotherapy. Targeted drug delivery, using liposomal drug delivery systems, is an attractive approach to enhance the efficacy of anticancer drugs and prevent side effects, thereby potentially increasing the therapeutic index. In most preclinical prostate cancer studies, passive liposomal targeting of anticancer drugs (caused by enhanced permeability and retention of the therapeutic compound) leads to an increased antitumor efficacy and decreased side effects compared to non-targeted drugs. As a result, the total effective dose of anticancer drugs can be substantially decreased. Active (ligand-mediated) liposomal targeting of tumor cells and/or tumor-associated stromal cells display beneficial effects, but only limited preclinical studies were reported. To date, clinical studies in prostate carcinoma have been performed with liposomal doxorubicin only. These studies showed that long-circulating, PEGylated, liposomal doxorubicin generally outperforms conventional short-circulating liposomal doxorubicin, stressing the importance of passive tumor targeting for this drug in prostate carcinoma. In this review, we provide an overview of the (pre)clinical studies that focus on liposomal drug delivery in prostate carcinoma.

Introduction on prostate cancer and liposomal drug delivery

Over the past decades, substantial progress has been made in the field of nanomedicinal drug delivery [1,2]. In this booming field, liposomes have taken a front-runner position and have been evaluated extensively in preclinical and clinical cancer settings. Meanwhile, a few liposomal formulations have been clinically approved for the treatment of cancer [3]. Among the extensive amount of studies in the field of liposomal tumor targeting, only a limited number of investigations have focused on the utility of liposomes in prostate cancer treatment. It is striking that amongst those studies, castration-resistant prostate cancer (CRPC) has deserved relatively little attention, as CRPC is one of the most detrimental among the advanced-stage cancers, with very little effective treatment options currently available. Many drugs designed for the treatment of CRPC fail at some point during clinical development due to intrinsic/acquired resistance and/or dose-limiting side effects. Described mechanisms for therapy resistance include overexpression of P-glycoprotein [4] and enhanced STAT1 expression [5]. Targeted drug delivery systems like liposomes may help overcome drug resistance as higher drug levels are potentially achievable at the tumor site. In addition, targeted drug delivery can diminish drug exposure of healthy tissues leading to less systemic side effects. In light of the extensive experience with several liposomal anticancer formulations [6], liposomal targeting of anticancer drugs to tumors in patients with prostate cancer seems a plausible drug targeting approach.

Liposomes are versatile, self-assembling, carrier materials that contain one or more lipid bilayers with phospholipids and/or cholesterol as major lipid components, and can be used to encapsulate hydrophilic drugs in their inner aqueous compartment(s) while more hydrophobic drugs can associate with the lipid bilayer(s) (Fig. 1) (reviewed in [7,8]). Compared to other nanocarriers, liposomes are relatively easy to prepare, biodegradable and essentially

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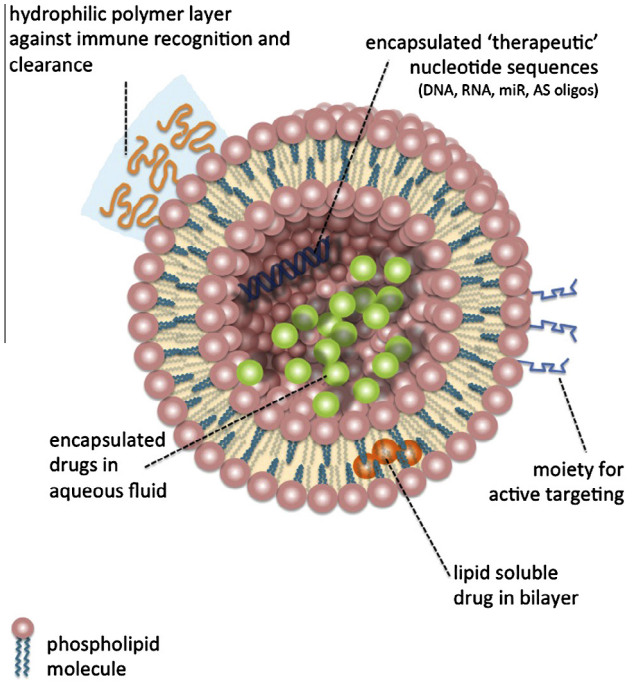

Fig. 1. Structure of a liposome used as drug delivery system.

nontoxic, although size is usually limited to 50–150 nm if used for drug delivery purposes [9,10]. Liposomes have been shown useful for drugs with unfavorable pharmacokinetic properties that result in a suboptimal therapeutic index. The addition of a polyethylene glycol (PEG) coating to the outer surface has been a major breakthrough as this coating opposes detection by the mononuclear phagocyte system (MPS) and thereby strongly enhances circulation time of intravenously injected liposome particles. As tumors often display a chaotic and highly permeable vasculature as a result of angiogenesis, the long circulation time of PEG-liposomes allows enhanced extravasation of liposomes into the tumor microenvironment compared to healthy tissues. Generally, an increased liposomal size favors extravasation as long as this size does not exceed the size of the inter-endothelial fenestrae, which are typically 200–400 nm [11–13]. After extravasation, liposomes are usually retained since lymphatic drainage is often impaired in tumors [7]. Hence, this tumor targeting mechanism is referred to as the enhanced permeability and retention (EPR) effect. Because no specific targeting ligands are used to interact with the tumor target site, this tumor localization process is referred to as 'passive targeting' and represents the major targeting principle for intravenously administered long-circulating liposomes (Fig. 2, upper left) [7,8]. Conversely, '*active targeting*' implies a ligand or antibody bound to the outer surface of liposomes that selectively target receptors/ligands overexpressed on the tumor cells (Fig. 2, upper right) or the (a)cellular tumor microenvironment (Fig. 2, lower left) [7,8,14]. Following binding to the receptor, internalization via receptor-mediated endocytosis can take place. Both the extent of tumor localization and subsequent cellular internalization determine the therapeutic efficacy of liposome-encapsulated anticancer agents [15].

The aim of this review is to summarize the literature on both passively and actively targeted liposomes for the treatment of prostate cancer, and to provide a perspective on the use of targeted liposomes as a new therapeutic option to treat this malignancy.

Preclinical studies

A limited number of studies focused on passive and/or active liposomal targeting of chemotherapeutic agents in preclinical prostate cancer models. Chemotherapy is widely used to treat prostate carcinoma, but is reserved only for the later stages of the disease, when the disease has progressed into the stage of CRPC for which typically a combination of docetaxel and prednisone is given [16,17]. Unfortunately, only a small proportion of patients respond to docetaxel and dose-limiting myelosuppression prohibits its intensification of treatment [16]. This unfavorable situation provides a strong rationale for tumor-targeted delivery of chemotherapeutic agents.

A phase I study with liposomal docetaxel was conducted in a cohort of multiple advanced solid malignancies which revealed higher maximum tolerated dosages of the liposomal formulation compared to free docetaxel (85 mg/m^2, or 110 mg/m^2 with G-SCF support; compared to 75 mg/m^2 for free docetaxel) [18]. Surprisingly, while being the standard-of-care for CRPC, liposomal docetaxel has not yet been investigated in preclinical models of prostate cancer. This is even more striking considering the range of studies that have been performed with liposomal formulations of other chemotherapeutic agents, including doxorubicin [19–23], gemcitabine [24,25], paclitaxel [26] and mitoxantrone [27].

Doxorubicin, an anthracycline widely used as chemotherapeutic agent, is associated with several side effects, most notably cardiotoxicity [28], and liposomal delivery of doxorubicin was proven useful to reduce chronic cardiotoxicity. As a result, liposomal delivery increases the therapeutic index of the drug. Indeed, liposomal doxorubicin has been clinically approved for the treatment of Kaposi's sarcoma, ovarian cancer, breast cancer and multiple myeloma (as PEG-liposomal doxorubicin marketed as Doxil in the USA and Caelyx outside the USA) and for advanced breast cancer (the non-PEGylated liposomal doxorubicin version marketed as Myocet) [3,29].

Passive delivery of liposomal doxorubicin was examined in multiple human prostate cancer cell line-based and primary prostate cancer-based *in vivo* models. Monotherapy with liposomal doxorubicin resulted in contrasting results, with three studies showing significant inhibition of subcutaneous tumor growth [19–21] while one study showed no effect [22]. It is hard to pinpoint the reason for these differential responses, as there were differences in liposomal compositions, size, tumor models, dosing and time of treatment. Liposomal delivery of gemcitabine, a nucleoside analog clinically used for several types of cancer, induced a potent antitumor effect which could only be matched by 45-fold higher doses of free gemcitabine (8 mg/kg/week versus 360 mg/kg/week, respectively) [24,25]. Moreover, decreased numbers of lymph node metastases were observed upon treatment with liposomal gemcitabine compared to free gemcitabine [25]. Liposomal delivery of mitoxantrone, the previous second-line treatment for CRPC, showed an inhibition of prostate xenograft growth but was not compared to free mitoxantrone [27].

In contrast to doxorubicin and gemcitabine, liposomal delivery of paclitaxel does not lead to a better outcome, as was evidenced by a study in a rat prostate cancer xenograft model. Here, efficient tumor inhibition by liposomal paclitaxel was observed at the cost of severe weight loss [26], indicative of excessive systemic toxicity. It may therefore be doubtful whether or not liposomal delivery will increase the therapeutic index of paclitaxel in advanced prostate cancer.

In the attempts to further enhance the efficacy of liposomal anticancer drug targeting, two approaches deserve attention: combination therapy and active targeting. Combination therapy of liposomal doxorubicin with radiation [19] or low frequency ultrasound [22] enhanced the antitumor efficacy compared to liposomal doxorubicin alone. In addition, ultrasound was shown to enhance the penetration of released doxorubicin throughout the prostate xenograft, thereby also reaching tumor cells further removed from the blood vessels [23].