

The Use of Nanocarriers for Drug Delivery in Cancer Therapy

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Abstract

The use of nanocarriers as drug delivery systems for chemotherapeutic agents can improve the overall pharmacological properties of commonly used drugs in chemotherapy. The clinical success, as well as the ease with which surface modifications can be made to both liposomes and micelles to accommodate targeting ligands have made these nanocarriers in particular attractive candidates for future work involving targeted drug delivery. Although not targeted, there are clinically approved liposomal-based drugs that are currently used to treat various types of cancers. Furthermore, there are several other formulations involving both of these nanocarriers which are now in various stages of clinical trials. This review discusses the use of liposomes and micelles in cancer therapy and attempts to provide some current information regarding the clinical status of several of these nanocarrier-based drugs. In addition, recent work involving the incorporation of targeting ligands to systems such as these in order to improve colocalization between the drug and cancer cells is also addressed. Furthermore, while the use of these nanocarriers in particular is the primary focus here, this review also contains a discussion on other commonly used nanocarriers in cancer therapy to include various polymer-based and polymer-protein conjugates. Finally, the possibility of using combinatorial approaches involving multiple surface modifications made to both liposomes and micelles in order to further improve their drug delivery capabilities is also discussed.

Keywords: Nanocarriers; Liposomes; Micelles; Drug delivery; Chemotherapy; Nanoparticles; Targeted drug delivery systems

Introduction

Cancer treatment involving chemotherapy is typically accompanied by toxic side effects, thereby limiting the amount of the drug that can be given to a patient. As a result, all of the tumor tissue may not be exposed to a lethal dose of the drug. The use of nanocarriers such as liposomes and micelles can improve the pharmacological properties of traditional chemotherapeutics. Their small size (~100nm or less) allows them to readily extravasate from circulation through vascular defects typically present at tumor sites due to ongoing angiogenesis (Maeda et al., 2000), where they can then deliver encapsulated cytotoxic agents to tumor tissue. This, coupled with the fact that there is generally poor lymphatic drainage at tumor sites, results in a phenomenon known as the enhanced permeability and retention (EPR) effect (Gabizon, 2001a; Matsumura et al., 2004), which in part explains their clinical success. For example, both DaunoXome and Doxil are examples of clinically-approved liposomal-based drugs that are currently used to treat either Kaposi's Sarcoma (Torchilin, 2007; Wang et al., 2008), or both ovarian and recurrent breast cancer (Allen and Cullis, 2004; Wang et al., 2008) (Table 1). Alternatively, micellar-based drugs containing doxorubicin, paclitaxel, or cisplatin are in various stages of clinical trials (Hamaguchi et al., 2007; Wilson et al., 2008; Valle et al., 2010) (Table 1).

While the use of both liposomes and micelles in cancer therapy seems promising, obstacles associated with drug transfer from these nanocarriers to tumor cells within the tumor site remain particularly challenging. The fact that these unmodified drug delivery systems are susceptible to opsonization while in circulation results in low tumor site accumulation. However, surface coating these nanocarriers with polyethylene glycol (PEG) allow for improved circulation times *in vivo*, and thereby the preferential accumulation of the drug within tumors (Gabizon, 2001a; Photos et al., 2003). As a result, various clinically approved nanocarrier-based formulations such as Doxil are PEGylated (M, 2000) (Gabizon, 2001b). In addition, PEG-lipids used as hydrophilic corona-forming blocks in many micellar-based drugs also allow for longer circulation times (Blanco et al., 2009). However, while the presence of the PEG moiety improves tumor

site accumulation of the drug, it also presents a steric barrier between the nanocarrier and tumor cells, which results in a dramatic reduction in tumor cellular uptake (Gabizon, 2001b; Hatakeyama et al., 2007). Therefore, delivery of the encapsulated chemotherapeutic is based on leakage in the tumor microenvironment, followed by the subsequent cellular uptake of the free drug. Further limiting the overall effectiveness of the drug is the fact that some cytotoxic agents commonly used in these formulations, such as doxorubicin, have limited tumor tissue penetrability following escape from its nanocarrier due to a high affinity between this drug and various components of the extracellular environment (El-Kareh and Secomb, 2005). Therefore, uniform distribution of the drug within the tumor microenvironment is not achieved, and all of the tumor tissue is not necessarily exposed to a lethal dose of the drug. As a result, many research groups are currently working on replacing this form of passive drug delivery with an active one in order to further improve the colocalization between the drug and cancer cells. This type of targeted drug delivery usually involves surface modifications made to these nanocarriers in order to accommodate surface ligands, which recognize and bind certain overexpressed receptors present on the cells of interest. While there are numerous nanocarriers available for such delivery, the use of liposomes and micelles is particularly ideal as surface modifications made to them eliminates the need for direct chemical conjugation between the drug and targeting moiety which is typically required with this form of delivery. This is a particularly important aspect associated with their use as conjugation of drugs directly to the targeting ligand can negatively affect the targeting molecule in a manner that disrupts receptor/ligand recognition

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Name	Nanocarrier	Clinical Status	Compound	References
DaunoXome	Liposome	Approved	Daunorubicin	50, 56
Doxil/Caelyx	Liposome	Approved	Doxorubicin	2, 50, 56
CPX-1	Liposome	P1	Irinotecan	4
LE-SN38	Liposome	P2	SN-38	31
MCC465	Ab-liposome	P1	Doxorubicin	38
NK911	Micelle	P1	Doxorubicin	27, 56
SP1049C	Micelle	P3	Doxorubicin	9, 27, 53
NK105	Micelle	P2	Paclitaxel	24
NC-6004	Micelle	P1/2	Cisplatin	57
Zoladex*	Polymer rods	Approved	Goserelin acetate	12
Lupron Depot*	Polymer microspheres	Approved	Leuprolide acetate	1, 12
Oncaspar	PEG	Approved	L-Asparaginase	11
PEG intron	PEG	Approved	α -Interferon	7
Zinostatin	Polymer	Approved	SMANCS**	42
PK1	HPMA copolymer	P2/3	Doxorubicin	48
Abraxane	Albumin	Approved	Paclitaxel	39
Ontak	IL2 Fusion Protein	Approved	Diphtheria toxin	15, 16
Zevalin	Anti-CD20	Approved	Yttrium-90/Indium-111	20
Bexxar	Anti-CD20	Approved	Iodine-131	20

*Polymers composed of polylactide-co-glycolide

**Styrene maleic anhydride neocarzinostatin

Table 1: Examples of nanocarrier-based chemotherapeutics that are either clinically approved, or in various stages of clinical trials for cancer treatment.

(Backer et al., 2004), and may alter the cytotoxicity of the drug (Chau et al., 2004; Kline et al., 2004). However, there are numerous other nanocarriers successfully used in cancer therapy, some of which also have targeting capabilities (discussed below).

This review discusses the use of both liposomes and micelles as nanocarriers for chemotherapeutics, and some current information regarding the clinical status of various drugs encapsulated within both of these drug delivery systems is provided. In addition, this review contains a discussion involving the incorporation of targeting ligands within these nanocarrier constructs in order to further improve overall drug delivery efficacy. While the use of these nanocarriers in particular is the primary focus of this review, the clinical success of other nanocarriers to include various polymer-drug and protein-drug conjugates is also discussed.

Liposomes

Liposomes contain an internal aqueous core used for drug encapsulation, which is surrounded by a phospholipid bilayer. The use of phospholipids is ideal as it relates to the biocompatibility of these nanocarriers. While the internal aqueous core is perfectly suited for the delivery of hydrophilic drugs, the phospholipid bilayer allows for the encapsulation of hydrophobic chemotherapeutics (New, 1990; Khan et al., 2008) (Figure 1A). In any event, encapsulation of the drug serves to minimize the unintended side effects of commonly used chemotherapeutics in liposomal-formulations such as cardiotoxicity that generally results with the use of anthracyclines (i.e. doxorubicin) (Rivera, 2003), and peripheral neurotoxicity commonly associated with the use of both cisplatin and vincristine (Wang et al., 2000; Bianchi et al., 2006). In addition, liposomes intended for cancer therapy are ~100 nm in diameter as this size allows them to extravasate from circulation through the leaky vasculature present at tumor sites, while at the same time retaining the ability to deliver a relatively large and effective dose of the chemotherapeutic to tumor cells (Siwak et al., 2002; Torchilin and Weissig, 2003a).

The clinical success of liposomes has made them a popular nanocarrier for future work involving targeted drug delivery. For example, while DaunoXome and Doxil are currently clinically approved, CPX-1 and LE-SN38 are examples of liposomal-based drugs that encapsulate a topoisomerase I inhibitor and are currently in Phase-II clinical trials for the treatment of colorectal cancer or colon cancer (Kraut et al., 2005; Batist et al., 2009) (Table 1). However, all

of these formulations are based on a passive form of delivery, and future work seeks to actively target tumor cells. In fact, MCC465 is a targeted liposomal-based drug currently in Phase-I clinical trials (Matsumura et al., 2004) (Table 1), and numerous other targeted liposomal-based formulations have recently been reported. For example, anti-HER2 immunoliposomes have been shown to be far more cytotoxic in HER2-overexpressing breast cancer cells than non-targeted liposomes (Gao et al., 2009). The cancer cell surface receptor CD44, which is found at elevated levels amongst various tumorigenic cells such as melanoma has also been the target of many liposomal-based strategies (Eliaz and Szoka, 2001; Rezler et al., 2007a). In fact, various liposomal formulations containing peptide sequences specific for certain upregulated integrins in both primary and metastatic melanoma have also been suggested (Rezler et al., 2007b). As the transferrin receptor is commonly overexpressed in various types of cancer, transferrin-coated liposomes have been developed and have been shown to be much more effective than their non-targeted counterparts (Li et al., 2009). More recently, anti-CD147 antibody-labeled liposomes containing doxorubicin have been shown to not only accumulate to a greater extent within various carcinoma cell lines with high expression of CD147 versus low expressers of this receptor, but also had a greater cytotoxic effect (Matsudaira et al., 2010).

Micelles

Micelles are colloidal dispersions constructed from amphiphilic molecules which tend to be ~20-80 nm in diameter. Their smaller size when compared to larger nanocarriers such as liposomes can limit their ability to carry a substantial dose of the chemotherapeutic agent to the tumor. However, this size still allows for renal filtration escape thereby allowing for adequate circulation times, and may have the additional benefit of increased tumor tissue penetration following extravasation when compared to larger liposomes (Blanco et al., 2009). The hydrophobic core found within micelles allows for the delivery of hydrophobic drugs (Figure 1B), which many chemotherapeutics tend to be. The solubilization of hydrophobic drugs also reduces the risk of drug aggregation during intravenous administration and potential embolism formation (Degim and Celebi, 2007). In addition, the hydrophilic micellar corona allows for increased circulation times *in vivo*, thereby allowing it to preferentially accumulate within tumors (Wang et al., 2005; Husseini and Pitt, 2008).

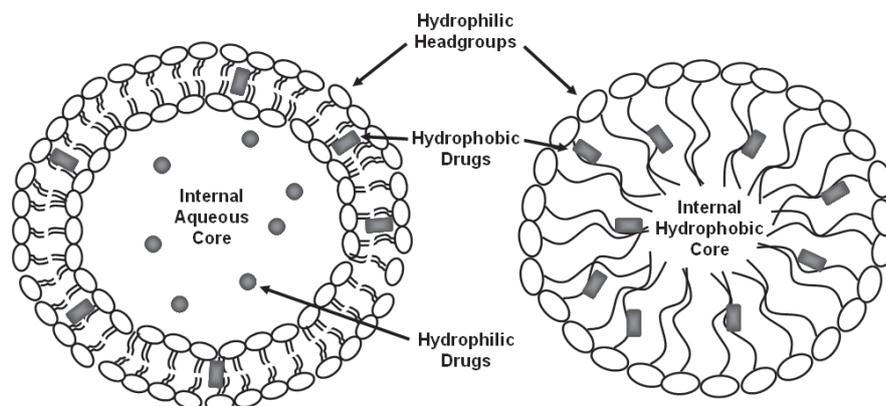


Figure 1: Schematic depicting the structure of liposomes which can accommodate both hydrophilic as well as hydrophobic drugs either in the internal aqueous core or phospholipid bilayer respectively (A), and the structure of micelles which can incorporate hydrophobic drugs within their internal hydrophobic core (B).

As with liposomes, micelles have also grown in popularity for use as a nanocarrier in cancer therapy, again partly attributed to the fact that there are also several micellar-based formulations currently in various stages of clinical trials. For example, NK911 and SP1049C are both examples of micellar-based drugs currently in Phase-I and Phase-III stages of clinical trials respectively (Danson et al., 2004; Kabanov, 2006; Wang et al., 2008; Valle et al., 2010) (Table 1). NK105 and NC6004 are also both micellar-based drugs currently in either Phase-II or Phase-I/II stages of clinical trials (Hamaguchi et al., 2007; Wilson et al., 2008) (Table 1). While encouraging, all of these formulations passively deliver chemotherapeutics to cancer cells, and future work involves targeting ligand addition within these constructs. These ligands include proteins (including antibodies), vitamins, as well as various carbohydrates (Nagasaki et al., 2001; Torchilin et al., 2003b; Licciardi et al., 2008). For example, immunomicelles containing a photosensitizing agent and tumor-specific monoclonal antibody have been successfully used in photodynamic therapy against murine lewis lung carcinoma (Roby et al., 2007). Micelles containing a folate moiety have been shown to be significantly more cytotoxic to ovarian carcinoma cells than non-targeted micelles (Kim et al., 2008). In fact, folate has also been successfully used recently as a targeting ligand in micelles to deliver poorly water-soluble chemotherapeutics (either tamoxifen or paclitaxol) to colon carcinoma cells (Licciardi et al., 2008). In addition, hyaluronic acid (HA)-paclitaxel conjugate micelles have recently been shown to be far more cytotoxic toward HA receptor overexpressing cancer cells than for HA receptor deficient cells (Lee et al., 2008).

Polymer-drug conjugates

While the use of both liposomes and micelles as drug delivery systems for chemotherapeutics have received much attention in cancer therapy, there are numerous other polymer-based nanocarriers that have experienced similar clinical success (Table 1). For example, Zoladex and Lupron Depot are composed of either small polymer rods or polymer microparticles respectively, and both entrap Luteinizing hormone-releasing hormone (LHRH) analogues in order to treat prostate cancer (Duncan, 2006; Agarwal et al., 2007). Both Oncaspar and PEG intron are PEGylated drugs used to treat acute lymphoblastic leukemia and various types of cancers respectively (Bukowski et al., 2002; Dinndorf et al., 2007). Zinostatin (Stimamler) is a polymer-protein conjugate, which is composed of the anti-tumor protein neocarzinostatin covalently linked to two styrene maleic anhydride polymer chains, and is used to treat hepatocellular

carcinoma (Okusaka et al., 1998). As far as promising new polymer-drug conjugates, PK1 is a nanocarrier-based system composed of N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer which is in Phase-II/III stages of clinical trials for the treatment of breast cancer (Duncan, 2006; Seymour et al., 2009).

Protein-drug conjugates

Another group of notable nanocarriers successfully used in cancer therapy involve protein-drug conjugates (Table 1) in which the protein used can act as the nanocarrier. For example, Abraxane which is classified as an antimicrotubule agent, is composed of albumin bound to paclitaxel and is currently used to treat metastatic breast cancer (Miele et al., 2009). A distinctive additional advantage associated with the use of some proteindrug conjugates is the ability to actively bind cancer cells, as is the case with the drug Ontak. It is a protein-drug conjugate in which a fusion protein is generated by combining sequences from IL-2 (specific for the CD25 component of the IL-2 receptor) with sequences from diphtheria, and is currently used to treat cutaneous T-cell lymphoma (Foss, 2000; Foss, 2001). Also, both Zevalin and Bexxar function in a similar manner, and are used to treat patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (Garber, 2002). It should be noted however, that while Ontak undergoes cellular internalization, both Zevalin and Bexxar do not as their target is the non-internalizing receptor CD20 antigen (Table 1).

Conclusions

The clinical success of various nanocarrier constructs in cancer therapy have made these and similar systems promising drug delivery vehicles for future work aimed to further improve their overall drug delivery efficacy. For example, the clinical success based on passively delivering chemotherapeutics encapsulated within both liposomes and micelles in cancer treatment have made these nanocarriers particularly attractive candidates for future work involving a more active form of delivery. This type of targeted drug delivery improves the colocalization between the drug and cancer cells based on modifications made to the nanocarrier thereby avoiding direct conjugation between the drug and targeting ligand, and many potentially successful constructs have been reported here.

While the use of some targeting ligands in nanocarriers may improve cellular internalization of encapsulated drugs (i.e. those that target receptors which undergo receptor-mediated endocytosis),

another challenge associated with this type of delivery is the release of the drug from the nanocarrier. This is due to the fact that cellular internalization of these nanocarriers generally results in them being sequestered to acidic endosomes (Lee and Tannock, 2006), which can result in drug protonation of weakly basic drugs such as doxorubicin (Gerweck et al., 2006). The result is that the encapsulated drug is unable to undergo nanocarrier/endosomal escape. However, a combinatorial approach in which surface modifications made to nanocarriers involve both a targeting ligand as well as a pH-triggered release mechanism following cellular internalization based on endosomal pH may in fact generate a very efficacious construct. Several pH-sensitive nanocarrier systems involving both liposomes and micelles have been described (Guo and Szoka, 2003; Gillies and Frechet, 2005). These constructs are designed such that they are stable while in circulation, but allow for triggered release of encapsulated material following cellular uptake based on endosomal pH. This type of combinatorial approach in nanocarrier design may in fact prove to someday be a very efficacious drug delivery system commonly used in cancer therapy.

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