

Lipoprotein based drug delivery: Potential for pediatric cancer applications

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Abstract

While survival rates for patients with childhood cancers have substantially improved, the quality of life of the survivors is often adversely impacted by the residual effects of chemo and radiation therapy. Because of

the existing metabolic and physiological disparities between pediatric and adult patients, the treatment of pediatric cancer patients poses special challenges to oncologists. While numerous clinical trials being conducted, to improve treatment outcomes for pediatric cancer patients, new approaches are required to increase the efficacy and to minimize the drug related toxic side effects. Nanotechnology is a potentially effective tool to overcome barriers to effective cancer therapeutics including poor bioavailability and non-specific targeting. Among the nano-delivery approaches, lipoprotein based formulations have shown particularly strong promise to improve cancer therapeutics. The present article describes the challenges faced in the treatment of pediatric cancers and reviews the potential of lipoprotein-based therapeutics for these malignancies.

Key words: Drug delivery; Lipoprotein; Nanoparticles; Pediatric cancers; High density lipoprotein

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Core tip: While survival rates for patients with childhood cancers have improved, the quality of life of survivors is often adversely impacted by the residual effects of therapy. Consequently, new approaches will be required to increase the efficacy and to minimize the drug related toxic side effects of pediatric cancer therapy. Nanotechnology is a potentially effective tool to improve cancer chemotherapy *via* enhanced bioavailability and specific targeting. Lipoprotein based formulations have shown particularly strong promise to improve cancer therapeutics. The present article describes the challenges faced in the treatment of pediatric cancers and reviews the potential of lipoprotein-based therapeutics for these malignancies.

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INTRODUCTION

Although cancer is the leading cause of death in children above 1 year of age in Europe and the United States, more than 80% of the children diagnosed with cancer are expected to survive, subsequent to treatment, though 40% will suffer through adulthood from the long term consequences of the treatment administered during childhood^[1,2]. While advances in the chemotherapy of pediatric malignancies have produced major improvements in survival over the last several years, treatment-related side effects remain a major concern.

The recently developed nanotechnology-based drug delivery vehicles (nano-DDVs) are directed toward overcoming the shortcomings of the currently employed chemotherapeutic agents, including poor solubility, limited bioavailability and inadequate stability^[3-6]. Additionally most of these nano DD systems target specific sites by either passive or active transport mechanisms^[7-10] and thus minimize the systemic exposure of normal tissues to the drug. Nanotechnology has also been shown to improve localized drug delivery by selective administration routes in order to overcome anatomical or physiological barriers, such as the blood brain barrier in the central nervous system^[11-13]. Currently available treatment modalities for pediatric malignancies involve chemotherapy, surgery, radiation, bone marrow transplant and immune based therapy. These treatments are often accompanied by short and long-term side effects, resulting in deterioration of physiological functions among the survivors that impact the quality of life well into adulthood^[14]. While current therapeutic approaches have markedly improved the prognosis for survival of pediatric cancer patients, a significant portion of childhood malignancies remain resistant to current regimens, leading to progressive disease and death^[15]. Hence there is an urgent need to develop novel therapeutic strategies for pediatric cancers, in addition to reducing the residual toxicities. This review aims to focus on the challenges involved in treating pediatric cancers and the potential for overcoming these barriers *via* nanotechnology in general, utilizing lipoprotein based nano DDV in particular.

PEDIATRIC CANCERS ARE DIFFERENT FROM ADULT CANCERS

Pediatric cancers are different from adult malignancies because they often originate from cellular populations that have not completed the process of terminal differentiation^[16-18]. Childhood cancers are often the result of genetic changes that take place very early in life, sometimes even before birth. Unlike many cancers

in adults, childhood cancers are thus not strongly linked to lifestyle or environmental risk factors. Accordingly, children are very rarely diagnosed with ovarian, breast, colon or lung carcinomas that frequently occur in adults. Although childhood cancers are often more aggressive and remain undetected until an advanced stage is reached, due to the advances in therapeutics over past decades pediatric cancers tend to be more easily curable than adult cancers. The most common cancers diagnosed in children are given in Table 1.

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute a 5-year relative survival rate for all cancers combined has increased from 61.7% in 1975-1977 to 81.4% in 1999-2006, among children from 0 to 19 years of age (NCI SEERS 2010)^[20]. Between 1975 and 2007 the mortality rates for non-Hodgkin lymphoma decreased by 75% followed by 60% reduction in mortality statistics for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)^[20].

As a result, non-Hodgkin lymphomas and ALL are now among the most curable childhood cancers. These improvements in the prognoses of selected malignancies can be attributed to the improved risk assessment, supportive care, the development of new drugs directed at specific targets and most importantly, enrollment of large numbers of patients in well-designed prospective clinical trials. However, the survival rates for children with other solid tumors, including most bone and soft tissue sarcomas and brain tumors have not improved as dramatically over past four decades.

THERAPEUTIC CHALLENGES IN PEDIATRIC ONCOLOGY

The differences between the metabolic capacity, drug bio-distribution, organ function and absorption in response to drug therapy of children and that of adults are well known^[21-23]. In addition, pediatric patients are less likely to have underlying health related issues as compared to adult populations undergoing treatment. The developmental changes profoundly affect the responses of children to medications and to related therapies^[24]. All these factors affect the way in which treatment modalities are designed and applied to pediatric populations.

Designing formulations for pediatric patients is often complex because this age group is further subdivided into different groups, based on differences in biology and metabolic capacity. These groupings represent preterm newborn infants, term newborn infants (0-27 d), infants and toddlers (28 d-23 mo), preschool children (2-5 years), school children (6-11 years) and adolescents (12-18 years)^[25]. Each sub-category displays different biochemical functions and capabilities^[18,24] while the level of cognitive development may also impact the effectiveness of drug formulations for cancer therapy^[26]. Because most pediatric cancers

Table 1 Frequently encountered pediatric malignancies^[19]

Type of cancer	Definition/characteristics	% Incidence 2005
Leukemia	Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system	34
Brain and central nervous system tumors	Normal cells in the brain or the spinal cord change and grow uncontrollably, forming a mass	23
Neuroblastoma	It is a neuroendocrine tumor, most frequently originating in one of the adrenal glands, in addition to nerve tissues in the neck, chest, abdomen, or pelvis	7
Wilm's tumor or nephroblastoma	Cancer of kidney that occurs in children	5
Lymphoma (Hodgkins and Non-Hodgkins)	Blood cell tumor that develops from lymphocytes	12
Rhabdomyosarcoma	Cancer of soft tissues where the cancer cells originate from skeletal muscle progenitor	3
Bone cancer	Osteosarcoma and Ewing's sarcoma are the most common malignancies of bone	4
Germ cell tumors	Germ cells tumors typically emerge from gonads but may also originate in other parts of the body, while arising from embryonic germ cell "rests"	N/A

N/A: Statistics not available.

are rare; hence sample size is often a major concern regarding the design and performance of clinical trials.

Clinical trials involving pediatric patients are further restricted by the hesitancy of ethical review committees toward drug trials in children and the reluctance of pharmaceutical companies to invest in these costly ventures in view of the limited children's pharmaceutical market. Another challenge faced by pediatric oncologists while designing clinical trials, is determining the appropriate dosages of a drug for administration, especially as they apply to combination therapy. Even though the mechanism of action and the effective dose of most drugs in adults are known, a linear dose-per-kg correlation may not be appropriate for small children. Kearns *et al.*^[24] reviewed key maturational changes that account for differences in drug metabolism and disposition of drug formulations in pediatric populations vs those in adults. Gastric emptying time, gastric and duodenal pH, intestinal transit time, secretion and activity of bile and pancreatic fluid, bacterial colonization and transporters, such as P-glycoprotein (P-gp) are important factors for drug absorption^[24], whereas key factors explaining differences in drug distribution between the pediatric population and adults are organ size, membrane permeability, plasma protein concentration and characteristics, endogenous substances in plasma, total body and extracellular water, fat content, regional blood flow and transporters such as P-gp, which is present not only in the gut, but also in liver, kidney, brain and other tissues^[23].

Cancer therapeutics *via* nano drug delivery vehicle (DDV) is an emerging field that is yet to be fully investigated in children. The toxicological aspects of the exposure to nanoparticles will need to be thoroughly assessed to establish their safety for children, before the application of these formulations in pediatric oncology. These challenges notwithstanding, the application of nano DDVs in cancer therapeutics represents one of the most promising and rapidly expanding approaches based on the number of research reports and clinical trials in progress. Consequently, it is likely that, in due time, nano DDVs will be broadly applied in pediatric

oncology.

Nanomedicine based therapeutics in children

The multiple advantageous features of nano DDVs, including high payload capacity, favorable biodistribution and pharmacokinetic profiles make them ideal candidates. Another advantage of most nano DDVs is their multimodal loading capability. The surface or core of the DDV may be loaded with multiple agents, so that treatment and monitoring of treatment *via* imaging can occur simultaneously (theranostics). Metals, chelators and/or radioisotopes may be included for CT and MRI or PET/SPECT imaging or *in vivo* imaging^[27-29]. The ease of tracking nano DDVs *in vivo*, presents a unique opportunity for monitoring drug distribution on a patient by patient basis to determine whether drug accumulation is sufficient for a desirable therapeutic effect.

The potential of using nanomedicine to improve the diagnosis and the treatment of pediatric cancers has been extensively documented^[30-32]. Several biologically based formulations have been applied in the form of nano DDVs^[33-38] (including cross-linked liposomes, lipids, chitosan, lactic acid conjugates, *etc.*^[36-38]) and chemical constructs (including polymer based, dendrimers, flo dots, quantum dots, ceramic, metal based, *etc.*).

As a result of research and development in nano DDV over past decade, several nano DDV formulations already made their way to the market including polymer-based poly(lactide-co-glycolide) nanocarriers, liposomes and abraxane^[39,40]. However, all of these formulations are designated for use in adults. Similar formulations are currently in different phases of clinical trials in pediatric populations (Table 2); however, none has reached the clinic yet.

LIPOPROTEIN BASED NANO DDVS

An ideal DDV is expected to have excellent loading capacity, therapeutic shielding, biocompatibility and selective targeting capability. An effective DDV formulation should also be able to accommodate multimodal

Table 2 Drug delivery formulations currently undergoing clinical trials for pediatric cancers

FDA approved Formulations	Drug	Phase of pediatric clinical trial	Type of cancer	Ref.
Abraxane	Paclitaxel	Preclinical	Rhabdomyosarcoma Osteosarcoma Neuroblastoma	[30]
Nab paclitaxel	Paclitaxel	Phase I and II	Rhabdomyosarcoma, neuroblastoma	[41]
Doxil	Doxorubicin	Phase I and II	Refractory or recurrent Rhabdomyosarcoma, Neuroblastoma, Pontine glioma	[31]
DaunoXome	Daunorubicin	Phase III	AIDS related Kaposi Sarcoma, pediatric in acute myeloid leukemia refractory / relapsed	[32]
L-Annamycin	L-Annamycin	Phase I	Acute lymphocytic and acute myeloid Leukemia	[42]
Depocyte	Cytarabine	Phase I	Acute lymphocytic leukemia	[43]
(liposomal formulation)			Recurrent brain tumor	[44]
Marquibo	Vincristine sulfate	Phase I Phase II	Sarcoma Neuroblastoma	[45]
CPX 351	Cytarabine and daunorubicin	Phase I	Relapsed leukemia or lymphoma	[46]

FDA: United States Food and Drug Administration.

anti-cancer and /or contrast agents (for tumor imaging) and exhibit minimum undesirable side reactions by avoiding interactions with off target sites. Lipoprotein-inspired DDVs possess most of these desirable features and thus represent a promising platform for pediatric cancer therapeutics^[35,47-50].

Lipoproteins are natural transport vehicles for shuttling lipids and lipophilic molecules in an aqueous milieu to organs of the body in mammals^[51]. Although there are several classes of lipoproteins differing in size, buoyant density and the constituent apolipoproteins present, they exhibit common chemical characteristics that include a hydrophobic core surrounded by an amphiphilic shell of a phospholipid/cholesterol monolayer and several apolipoproteins. There are four major classes of lipoproteins present in the human/mammalian circulation (Figure 1), including chylomicron (75-1000 nm/ApoB-48), very low density lipoprotein (30-80 nm/ApoB-1000), low density lipoprotein (LDL) (18-25 nm/ApoB-100) and high density lipoprotein (HDL) (5-12 nm/ApoA-I, A-II, -E and -C)^[47,52,53]. Due to their unique structural/functional properties lipoproteins are considered an excellent model DDVs for transporting and delivering chemotherapeutic agents^[47].

Lipoprotein DDVs may be artificially assembled in different ways to transport drugs or imaging agents to desired sites^[34,35]. Depending on the chemical nature of the payload and the method of formulation these DDVs may be loaded either by covalent modification of the phospholipid or protein component, intercalation of the agent into phospholipid or encapsulation into the hydrophobic core of the DDV^[47,54,55].

Drug delivery via LDL and HDL receptors: Carcinogenesis is a multifaceted process that involves immense reorganization of signaling pathways, genetic information, structural constituents and energy

metabolism of the cell^[56,57]. As a result, cancer cells exhibit markedly elevated metabolic/energy requirements to sustain the tumor proliferation and migration functions^[58]. These changes are induced and facilitated by mutating growth factor receptors resulting in constitutive signaling to key metabolic pathways^[50,59]. In addition to basic nutrients, cancer cells have an excessive need for many other substances including cholesterol for membrane biogenesis^[60]. One of the mechanisms that cancer cells use to meet this requirement is by over-expressing the LDL and HDL lipoprotein receptors^[59,61-63]. Drug delivery strategies have been developed using both LDL and HDL receptor targeting DDVs^[64-67] as well as liposome DDVs modified by LDL receptor ligands^[68,69]. The drug carrying reconstituted HDL (rHDL) nanoparticles targeted to Scavenger receptor B-1 (SR-B1) function as a "magic bullet" and enhance the therapeutic efficacy of the enclosed drugs toward malignant tumors^[70]. The over-expression of the SR-B1 receptor in malignant tissues has the potential to facilitate the enhanced selective delivery of anti-cancer agents to tumors thus providing a marked improvement of the current chemotherapy regimens, including the limiting of off-target toxicity^[59,61,62].

Why use the rHDL nanoparticles for drug delivery of anti-cancer drugs in pediatric oncology?

While numerous studies employed liposomes to produce improved solubility and bioavailability of anti-cancer agents, due to their small size, rHDL nanoparticles accrue substantial additional therapeutic benefits (Figure 1) *via* their enhanced capability to penetrate the tumor microenvironment, including its vasculature and stroma. This is anticipated to be a major advantage when treating pediatric cancers since these tumors are often associated with stroma. The rHDL DDVs have

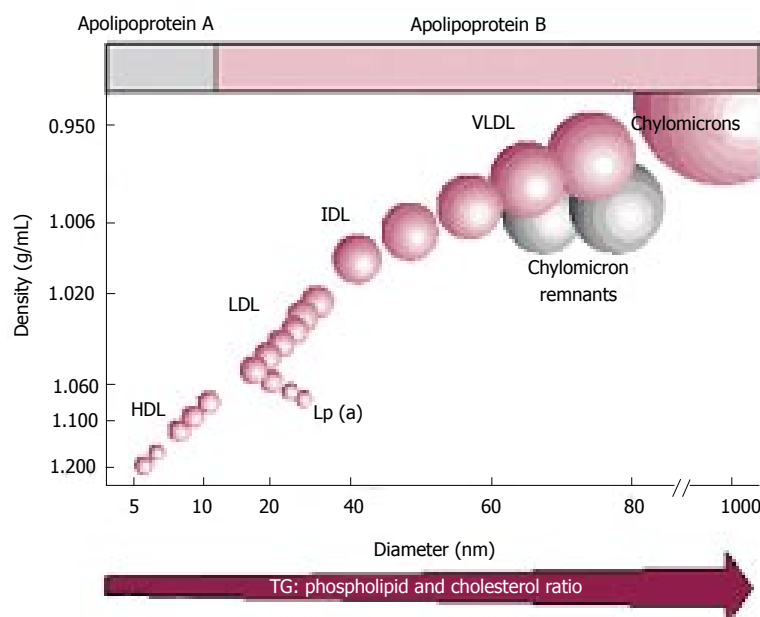


Figure 1 Size and density distribution of lipoproteins. HDL: High density lipoprotein; IDL: Intermediate density lipoprotein; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein.

been evaluated regarding their efficacy and capacity to perform targeted delivery of cancer drugs^[61,62,71]. In addition, the rHDL DDVs are comprised of endogenous biocompatible ingredients that have already been injected into human subjects during cholesterol metabolism trials^[72].

Due to their structural similarity to their natural counterparts, rHDLs effectively avoid recognition by the reticuloendothelial system that clears foreign substances, and thus fail to trigger immune responses in contrast to other synthetic DDVs including liposomes^[73]. Additional advantages of the rHDL DDVs include extended retention time in circulation, stability and cytoplasmic drug delivery to circumvent drug resistance that may develop during chemotherapy. Also lesser amounts of drug are likely to be required for achieving the same cytotoxic effect compared with the drug used in its free form^[67]. Although these advantages of lipoprotein based nano DDV could be beneficial to all types of cancer patients, pediatric patients are anticipated to benefit the most by the extended safety, long drug retention time and enhanced therapeutic efficacy.

Our laboratory has focused on studies of targeted drug delivery, including optimization of the rHDL nanoparticle *via* attachment of targeting molecules. Mooberry *et al.*^[61] have shown that the uptake of paclitaxel by ovarian cancer cells from rHDL DDVs could thus be substantially enhanced by covalently attaching a folic acid residue to the apolipoprotein component of the nanoparticle. Similarly, Parker *et al.*^[74] exploited the overexpression of folate receptors in tumor cells by conjugating folic acid to the apolipoprotein B component of an LDL-like DDV and thus specifically targeted drugs, transported by the lipoprotein vehicle. These studies suggest that lipoprotein DDVs could be specifically functionalized for targeting surface antigens (including receptors) that are overexpressed by malignant

tumors^[48,60]. Overall, as described above, lipoproteins possess many desirable characteristics that enable them to serve as natural or synthetic drug transporters. While lipoproteins were proposed as efficient DDVs over thirty years ago, perhaps surprisingly, no lipoprotein formulation has so far been approved for clinical application to date. The recent upsurge in interest to develop lipoprotein DDVs will perhaps spawn the needed energy and investment to fully take advantage of this robust, natural drug carrier for therapeutic purposes in general and pediatric formulations in particular.

FUTURE PERSPECTIVE FOR PEDIATRIC CANCER CHEMOTHERAPY

Conventional cancer chemotherapy has traditionally been associated with undesirable side effects that are especially troublesome during the treatment of pediatric patients. Researchers have drawn attention to the multidimensional benefits of lipoprotein based DDVs including their biocompatibility and stability that enable them to minimize these side effects *via* specifically targeting malignant cells and tumors while avoiding normal tissues^[48,59,61,63,75]. Several clinical studies have demonstrated that HDL-type formulations have been safely administered to human subjects^[76-78]. Selection of patients for rHDL driven chemotherapy could be based on the SR-B1 expression levels of each specific tumor involved; thus, provide a new bio-marker for eventual personalized therapy. There are numerous additional membrane proteins which could be used as targets for functionalized rHDL. This feature of rerouting DDVs from their endogenous receptors and steering them to specific sites^[71] could further enhance the potential of the rHDL nanoparticles to facilitate the development of a robust personalized therapy regimen for pediatric cancers. Despite the major advances in

pediatric cancer research, there are several malignancies afflicting children that remain resistant to therapy. In addition, extension of 5 year survival or even producing permanent remission is often accompanied by harmful long lasting and debilitating side effects in pediatric cancer patients. Perhaps improved treatment modalities developed *via* novel nanoparticle formulations and specifically involving lipoprotein type carriers will provide the needed tools to overcome the current barriers to successful pediatric cancer therapy.

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