

Therapeutics and Toxicology of Liposome-Based Anticancer Drugs

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Most of the currently used anti-tumor agents have problematic toxicities compromising efficacy, and often resulting in life-threatening events. Liposomes can provide effective control of the release rate and of the tissue distribution of many of these agents. These pharmacokinetic changes often have a major pharmacodynamic impact with attenuation of toxic effects and protection of sensitive tissues from dangerous and unwanted drug exposure. Polyethylene-glycol (PEG) coating of liposomes results in inhibition of liposome uptake by the reticulo-endothelial system and significant prolongation of liposome residence time in the blood stream. A hallmark of these long-circulating liposomal drug carriers is their enhanced accumulation in tumors. The mechanism underlying this passive targeting effect is the phenomenon known as enhanced permeability and retention (EPR) which has been described in a broad variety of experimental tumor types, and appears also to be a relevant phenomenon in human cancer. Developments in drug loading technology have improved the efficiency and stability of drug entrapment in liposomes, particularly with regard to anthracyclines, vinca alkaloids, and camptothecin analogs. Coupling the advances in liposome engineering such as pegylation with highly efficient drug remote loading techniques has resulted in robust formulations with great improvements in pharmacokinetics and pharmacodynamics over the conventional administration of cytotoxic drugs.

An example of liposome formulation with demonstrated clinical added value is pegylated liposomal doxorubicin (PLD), which has demonstrated clinically a favorable safety profile and proven efficacy against various malignancies and can be considered as the first anti-cancer nanomedicine approved for clinical use. The clinical pharmacokinetic profile of PLD is characterized by slow plasma clearance and small volume of distribution with drastic shifts (~1000-fold) from free doxorubicin. Based on preclinical studies, other formulations such as pegylated liposomal irinotecan hold promise to offer an important clinical edge in cancer chemotherapy. Another type of approach applicable to liposomal drug delivery combines the concept design of a stable and long-circulating liposome with chemical modification of a drug to provide a lipophilic prodrug with strong association to the liposomal bilayer. This is the case of a prodrug of mitomycin-C activated by thiolytic cleavage. Thiolytic cleavage takes place in the tissue micro-environment with negligible activation in plasma thus preventing drug activation and drug leakage in the blood stream and resulting in 3-fold decrease in toxicity when compared to treatment with free mitomycin-C.

Further to the passive targeting effect, the liposome drug delivery platform offers the possibility of grafting tumor-specific ligands on the liposome membrane for active targeting to tumor cells, and potentially intracellular drug delivery. Ligand-specific targeting may enhance tumor drug accumulation and reduce further the toxicity of liposome-delivered drugs in comparison to passively targeted systems.

Liposome-based systems offer a vast array of potential applications in the delivery of cancer chemotherapeutic agents. Provided liposome composition and drug entrapment are properly engineered, major changes in the pharmacokinetics and biodistribution can be obtained. Pharmacodynamic changes may result in a substantial improvement of the toxicity profile and in a significant enhancement of the therapeutic index of the entrapped drug. Although liposomal doxorubicin has already found a place in routine clinical use, the potential of liposomal drug delivery remains so far under-exploited.