

Cancer Therapy with Drug Delivery Systems

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Introduction

In today's day and age, various drug delivery systems have evolved along with the development and research of varied chemotherapeutic agents to ensure safer delivery of these agents to achieve optimal clinically efficacious response. Currently used anticancer drugs suffer from a myriad of problems such as extremely low aqueous solubility, lack of stability, nonspecific drug accumulation, which eventually leads to toxicity issues. Additionally, low bioavailability along with organ toxicity causes a major limiting factor for the maximum tolerated dose. These combinations of drug delivery systems along with the chemotherapeutic agents have led to the alleviation of multiple indications in various cancers, thus leading to a more clinically enhanced response, as compared to the chemotherapeutic agents alone [1]. One of the classic examples is liposomal Doxorubicin used to treat AIDS-related Kaposi's sarcoma and ovarian cancer which has undergone clinical approval [2,3]. Other drugs encapsulated in liposomes are currently undergoing clinical trials or have been approved for clinical use such as Daunoxome (Liposomal Doxorubicin) used to treat AIDS-related Kaposi's sarcoma [4,5] or Depocyt (Liposomal Cytarabine) used to treat lymphomatous meningitis [6]. Other approved products include Abraxane (Albumin bound Paclitaxel) used to treat metastatic breast cancer [7] and Marqibo (Liposomal Vincristine) used to treat acute lymphoblastic leukemia [8]. Other approved products include Genexol-PM [(Methoxy-PEG-poly (D,L-lactide) taxol] which has been approved in S. Korea for metastatic breast cancer and Oncaspar (PEG-L-asparaginase; Enzon) which was approved by FDA in 2006 for Acute Lymphoblastic Leukemia.

Nanoparticulate Systems in Tumor Targeting

Nanoparticles will be able to deliver a precise dose of the drug in the tumor region due to the enhanced permeability and retention effect. General features of the tumors include leaky blood vessels and extremely poor lymphatic drainage. Free drugs are known to diffuse non-specifically; however, nanoparticles accumulate at the specific target site with the aforementioned enhanced permeability and retention effect.

With the aid of optimized targeting ligands on their surface, nanoparticles will be able to deliver the payload at the tumor site and even reduce its distribution to the peripheral tissues. For example, in a breast cancer model, a receptor density of 10^5 copies of ErbB2 receptors per cell is an optimal number by which the therapeutic efficacy of an anti-ErbB2 targeted liposomal doxorubicin can be increased vis-avis its non-targeted counterpart [9]. It is extremely vital to select the appropriate kind of polymer as its essential inherent characteristics such as exact polymer composition, hydrophobicity, its degradation profile along with the drug's oil-to-water partition co-efficient and its mode of localization, incorporation or adsorption will ultimately affect the drug distribution pattern *in vivo* [10]. Liposomal-based nanocarriers are known to be prone to extreme challenges that are encountered in their development and overall stability. Polyethylene Glycol (PEG) has been reported to increase the circulation times by affording them protection

from opsonization [11]. However, certain exceptions exist in the form of approved products such as Daunosome and Myocet (without PEG coating) that have been known to demonstrate improved circulation times [12]. Certain nanoparticles such as polymeric micelles have also been researched extensively in cancer therapeutics for delivering the drug precisely to the target site, with favorable pharmacokinetic parameters and improved toxicity profile [13,14]. These micelles are self-assembling closed lipid monolayers with a hydrophobic core and a hydrophobic shell. They are classified under a group of amphiphilic colloids and can be formed above specific concentrations (Critical Micellar Concentration) and above specific temperatures (Critical Micellar Temperatures). One of the classic examples in clinical trials is NK911, a block copolymer of PEG and polyaspartic acid and a bound doxorubicin fraction for metastatic pancreatic cancer treatment [11]. Another example of micellar nanoparticle is NK105, consisting of paclitaxel which was investigated for pancreatic, colonic and gastric tumor treatment [15]. As a result of the high surface area to volume ratio of these nanoparticles; it is quite possible to achieve high ligand density on the surface of these nanocarriers for active targeting purposes. Controlled release of the drug from these nanocarriers is another important parameter which determines the fate of drug in the body, once the drug-loaded nanocarriers are administered. Till date, not less than 12 drug-polymer conjugates have entered Phase I and II clinical trials for targeting blood vessels in tumors. Despite the myriad drug targets and a host of chemistries available, only four drugs namely Doxorubicin, Camptothecin, Paclitaxel and

Platinate and some polymers such as Polyethylene Glycol (PEG), poly-L-glutamic acid, (N-(2-hydroxypropyl)methacrylamide (HPMA) and Dextran have been often used to develop polymer-drug conjugates [16].

Conclusion

The choice of optimal nanocarriers has to be extremely judicious considering its overall pharmacokinetic profile and factors which may influence the efficacy and biodistribution of the delivery system. Developing robust methods for high throughput screening of these nanocarriers is extremely laborious and time consuming. In addition, strategies have to be designed in the initial phases to avoid the uptake of these nanocarriers by the Reticulo-Endothelial System (RES). However, because of the diligent investigative research, a large number of clinical

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trials are underway with various antibody containing nanocarriers formulations. Biological targets, whether it be cell surface markers or tumor vasculature or the extracellular matrix surrounding the tumor microenvironment always pose monumental challenges. An optimistic era of research will usher in significant amounts of progress in both the diagnostic and therapeutic potential of these nanocarriers.

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