Challenges in Nanodrug Tumor Delivery: RES Uptake, Toxicities, and Bioavailability

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PERSPECTIVE

Nanodrugs can accumulate in tumors via the Enhanced Permeability and Retention editor (EPR) effect, which is one of the extensively explored strategies for anti-cancer drug delivery [1]. Seven anti-cancer nanodrugs, i.e., Abraxane, DaunoXome, DepoCyt, Doxil, Marquibio, Oncaspar, and Onivyde, have been approved for clinical use. Encapsulation of therapeutic molecules (e.g., small molecule inhibitors, siRNA, aptamers, etc.) in nanomaterials can improve the drugs’ solubility and blood circulation, alter their biodistribution, decrease their toxicities, overcome drug resistance, and also can facilitate entry into the target cell. However, only a small percentage of these nanodrugs accumulate even in high-EPR xenografted tumors (less than 1% according to a recent meta-analysis study) [2]. A major proportion of nanodrugs are taken by the Mononuclear Phagocytic System (MPS) or Reticuloendothelial System (RES), especially by the liver and spleen. In this Perspective, we discuss the current strategies and progresses for decreasing the RES uptake and the related toxicities and for increasing the delivery of anti-cancer nanodrugs.

“Stealth” coating of nanodrugs is one major achievement in the field of drug delivery and the first “stealth” nanoparticle can be dated back to 1977 [3]. Nanoparticles may “escape” the RES by coating the particle’s surface with hydrophilic polymers/surfactants, and/or formulation with biodegradable copolymers with hydrophilic segments, such as Polyethylene Glycol (PEG), poloxamer, poloxamine, polyethylene oxide, dextrane, and polysorbate 80 (Tween 80) [4,5]. PEG is the most commonly used non-ionic hydrophilic polymer to make “stealth” nanoparticles in order to reduce the RES uptake and increase the blood circulation of the nanoparticles. The first approved PEGylated product, Doxil (doxorubicin HCl liposome injection), has already been in the clinic for ~25 years [6,7]. Recently approved Onivyde (irinotecan liposome injection) is also a PEGylated liposome [8]. Other modifications of the nanoparticle characteristics and surface properties, such as size, shape, charge, composition, and tumor targeting moiety might also decrease RES uptake and increase tumor delivery. However, with all the above efforts, the current status of using anti-cancer nanodrugs is that a very small fraction (0.7%, median) of the injected nanodrugs is delivered to solid tumors [2].

Decoy systems have been tested to decrease the RES uptake and increase the targeting by Lanza and Wickline in 2005 [9]. This method comprises administering...
simultaneously a nanoparticle (imaging agent or therapeutic agent) in the presence of an excess of untargeted carrier, or decoy. The inactive carrier-decoy composition is administered simultaneously with a targeted carrier composition that contains vehicles for delivering a desired agent to a biological target. This simultaneous administration enhances the delivery of the targeted composition to the desired location in a subject. The decoy must mimic the behavior of the targeted nanoparticle. The inactive carrier decoy and the biocompatible nanoparticle need to share similar “non-active” part of the active nanoparticle or the compound of interest. According to this decoy strategy, each active nanoparticle shall have its own empty nanoparticle as the decoy, which needs additional FDA approval for clinical use.

Recently, studies were conducted to investigate the effect of Kupffer cell depletion on nanodrug delivery [10,11]. Since the major obstacle to the long-term circulation and delivery of nanodrugs is clearance by the Kupffer cells, the authors used clodronate liposomes to remove the Kupffer cells. This is an effective method to deplete Kupffer cells and address their functions for nanodrug delivery, but we have certain concerns that clodronate liposomes will deplete all types of monocytes/macrophages in the body, including the tumor associated macrophages, which might affect some properties of tumor. It is important to note that clodronate liposomes are not a FDA approved agent.

With clodronate liposomes to deplete Kupffer cells, tumor delivery of the nanodrugs increased up to 150 times. However, the maximum delivery efficiency was only 2%! Depletion of Kupffer cells can achieve long-term circulation of the nanodrugs, but 98% did not accumulate in the tumor [10]. Later, it was shown that the removal of Kupffer cells increased fecal elimination of nanodrugs by >10 times [11].

These studies point out that anti-cancer nanodrug tumor delivery is much more complicated than we thought. Facing all the challenges, we first need to understand how nanodrugs are eliminated from the body. We need in-depth knowledge of the heterogeneity of cancers and biological factors that influence the behavior of a nanodrug towards a tumor. In addition to EPR effect, tumor targeting ligands are critical to increase the delivery. For all the necessary studies, an appropriate animal model and testing protocol are highly desired.

We have developed a strategy to temporarily blunt the RES uptake of nanoparticles, instead of chemically depleting Kupffer cells, by using an FDA approved lipid emulsion, Intralipid. Intralipid is the brand name of the first safe fat emulsion for human use, approved in 1972. Intralipid 20.0% is composed of 20% soybean oil, 1.2% egg-yolk phospholipids, and 2.25% glycerol and manufactured by Fresenius Kabi (Uppsala, Sweden). The major fatty acid constituents are linoleic acid (44-62%), oleic acid (19-30%), palmitic acid (7-14%), linolenic acid (4-11%), and stearic acid (1.4-5.5%). We have tested our strategy by using nano- and micron-sized MR imaging agents [12], an in-development dichloro (1, 2-diaminocyclohexane) platinum (II)-loaded and hyaluronic acid polymer-coated nanodrug (DACHPt/HANP) [13,14], and FDA approved anti-cancer nanodrugs, e.g., Abraxane, Marqibo, and Onivyde [15], as shown in Figure 1. The animals (rats) were treated with Intralipid (2 g/kg, clinical dosage) intravenously (clinical route) 1-hr prior to and 24-hr post the injection of the nanodrugs. We have found that our methodology can be very useful to decrease the RES uptake of the nanoparticles and increase their bioavailability [12,13]. For example, Intralipid can reduce platinum accumulation in the liver, spleen, and, interestingly, kidney by 20.4%, 42.5%, and 31.2% at 24-hr post DACHPt/HANP administration, respectively. The bioavailability of DACHPt/HANP increases by 18.7% and 9.4% during the first 5 and 24hr, respectively. We have also found that DACHPt/HANP, Abraxane, Marqibo, and Onivyde exhibit different toxicity profiles. Intralipid can reduce the drugs’ toxic side effects in the RES and kidney in different levels [13,15]. Intralipid methodology could be a valuable complement to the above “stealth” strategies, to reduce the RES uptake on anti-cancer nanodrugs. This approach is a general one, unlike the decoy method, applicable to any approved and in-development nanodrugs without additional modification of the nanoparticles and the drugs.

Through our Intralipid methodology, we hope that we can give physicians more options to treat cancer patients with these powerful nanodrugs. A critical limitation in the current delivery of the anti-cancer drugs to patients is the amount of these cytotoxic drugs that a patient can tolerate. Since Intralipid can reduce the off-target toxicities in multiple organs, a physician
could increase the dosage of a nanodrug to kill as many cancer cells as possible. If the Intralipid treatment can improve the bioavailability of the drug as shown in DACHPt/HANP, thus can improve the delivery of the drug, a physician could reduce the dosage of the drug, which is very expensive, without affecting the efficacy of the drug. Thus, our findings for the use of Intralipid with nanodrugs can lead to the improvement of the quality of life for patients who undergo the therapeutic treatment as well as to the reduction of healthcare costs.

Figure 1: Intralipid reduces the toxicity and improves the bioavailability and biodistribution of anti-cancer nanodrugs. Modified from Figures 1 and 7 of Liu et al [13] and Table 1, Figures 3, 4, and 5 of Liu et al [14].

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REFERENCES