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Perspectives on Clinical Translation of Smart Nanotherapeutics

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Introduction

Smart nanocarriers have shown great promise in the delivery of various therapeutic payloads to primary and metastatic tumor sites via enhanced permeability retention (EPR) effect [1-4]. To be efficacious, cancer nanotherapeutics need to have the following characteristics: (1) the nanocarriers need to be biodegradable and non-toxic; (2) scale up synthesis is feasible and formulation protocol in the clinic by the pharmacist is convenient, (3) the nanocarriers need to be highly stable in the blood circulation, with minimal premature drug release; (4) to minimize uptake by the reticuloendothelial system in the liver, spleen, lung and bone marrow, the nanoparticle drugs need to be small (<100 nm in diameter) and with “stealthy” surface; (5) delivery of the nanoparticle drug into the tumor sites needs to be high and sustained; (6) efficient uptake of the drug-loaded nanoparticles into the tumor cells enhances efficacy and overcomes drug resistance; (7) efficient drug release from the nanocarriers at the tumor site or inside the tumor cells ; and (8) drug release from the nanocarriers triggered on demand allows the oncologists to tune the therapeutic index to the patient's advantage.

Biodegradable and non-toxic

Since most hard nanoparticles are not biodegradable, acute and long-term toxicity of these agents are of concern. It is unlikely that quantum dots comprised of toxic material such as CdSe, even if encapsulated with inert polymer, will ever be approved for *in vivo* clinical applications. Gold, iron or possibly silica are probably less toxic but they are not easily

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biodegradable. “Soft” nanoparticles like polymer-based micelles or dendrimers are generally biodegradable and then are metabolized and removed by the liver and kidneys. Depending on chemical composition, some soft nanoparticles can be very toxic [5-7]. It is therefore very important to understand the biodistribution of the nanocarriers and their components to ensure that they are biodegradable and that they are not toxic to the patient.

Minimal premature drug release into the circulation

Many nanocarriers may be stable in saline but after i.v. administration, these nanocarriers will encounter many different blood components, some of which could be detrimental to their stability, leading to premature drug release. For example, drug loaded micelles, unless crosslinked covalently, will dissociate upon interaction with lipoprotein particles (HDL, LDL, VLDL and chylomicron) ubiquitously present in the blood. We have recently used electron paramagnetic resonance studies with spin-labeled telodendrimers to demonstrate that covalent crosslinking of the micellar components avoids dissociation of the nanocarrier and premature drug release. It is clear from the few *in vivo* studies reported in the literature that reversibly crosslinked micelle can alleviate the problem of premature drug release and therefore significantly improve their therapeutic efficacies [8-12].

Minimal reticuloendothelial uptake

To minimize uptake into the reticuloendothelial system of liver, spleen, lung and bone marrow, the nanocarriers need to be smaller than 100nm in diameter. Large nanoparticles tend to cumulate in the liver and lung. Systematic study with micellar nanoparticles decorated with varying number of acidic and basic amino acids on the surface suggests that liver and lung uptake can be minimized by incorporating slightly negatively charged residues to the nanoparticle surface [13, 14].

Tumor targeting

Although nanoparticle drugs less than 100nm diameter, even without targeting ligands, can be preferentially taken up by tumor via EPR effects, it has been demonstrated in xenograft models that the addition of tumor targeting ligands to the nanoparticle drug can enhance anti-tumor efficacies [9, 15, 16]. Some ligands can induce receptor-mediated endocytosis, leading to the delivery of high concentration of drugs inside the tumor cells, and perhaps escape drug efflux caused by the P-glycoprotein, thus overcoming drug resistance.

Most of the published work on reversible crosslinked nanocarriers relies on the reductive microenvironment inside the cancer cells or the acidic pH within the endosomes of the target cells [8-12]. Therefore, to be fully efficacious, the nanoparticle drugs need to be delivered inside the target cancer cells. This can be achieved with nanocarriers decorated with cell surface targeting ligands or antibody molecules that facilitate endocytic uptake [17-19].

On-demand drug release

We reported on the use of on-demand cleavable linkers to crosslink the nanocarriers. This not only minimize premature drug release in the circulation, but also allows one to

administer exogenous cleavage agents at the desired moment to trigger drug release at the target tissue for enhancing therapeutic effects [9, 10]. In the murine ovarian cancer xenograft model, administration of N-acetyl cysteine (a reducing agent) twenty-four hours after each dose of paclitaxel-loaded micelle is superior to paclitaxel-loaded micelle alone [9]. For human applications, the optimal time to give the cleaving agent will need to be worked out.

Scale up synthesis and convenient formulation protocol in the clinic

Preparation of nanocarriers at the laboratory scale have been reported by many investigators. Once they have been proven to be efficacious in xenograft models and non-toxic in two mammalian species, preparation of these nanoparticle drugs needs to be scaled up for Phase I clinical trials. For some nanoformulations, scale-up synthesis may be very difficult if not impossible. For successful clinical translation, scale-up production of the nanoparticle drugs needs to be economical, reproducible and robust. Shelf-life of the nanoparticle drugs needs to be measured in months, not days or hours. Range of particle size needs to be narrow. Importantly, reconstitution protocols in the clinic needs to be very simple and reproducible. Ideally, the drug-loaded nanoparticles are prepared in lyophilized form with a shelf life of at least one year, and what the pharmacist needs to do in the clinic is simply to reconstitute it with water or normal saline and gentle mixing prior to administration to the patients.

Route of administration

The most common route of administration of nanoparticle drug is intravenously [20-22]. This allows systemic delivery of the nanoparticle drug throughout the blood stream but preferential uptake by the primary and metastatic tumors via EPR effects. The EPR mechanism, however, may not be applicable to small metastatic lesions with few blood vessels. Additional therapies that can reach these small metastatic lesions will be needed. These include free drugs, ligand-drug conjugates or antibody-drug conjugates.

For tumors that are confined regionally, e.g. Stage III ovarian cancer, where the tumor is present within the abdominal cavity, one may give the nanoparticle drug both intravenously and intraperitoneally. In fact, combination intravenous and intraperitoneal administration of paclitaxel is a common practice for this disease [23]. Intra-tumoral injection of nanoparticle drug under CT-guidance is feasible, and the nanoparticles are expected to be retained at the tumor sites longer than free drugs. This may be useful for the treatment of regional disease but not for patients with multiple metastatic lesions. Intra-tumoral injection of nanoparticle drug may also be useful for the treatment of primary brain cancer as treatment options for this dreadful disease are very limited. Pulmonary inhalation of nanoparticle drugs is certainly useful for benign pulmonary diseases such as asthma. It may also be an alternative route for the treatment of lung cancer or tumor metastasis to the lung, but this will need to be studied.

Intra-thecal chemotherapy is routinely administered to patients with acute lymphocytic leukemia and selected patients with lymphoma. This is given for prophylaxis against tumor metastasis to the central nervous system. Intra-thecal chemotherapy is also given to patients with meningeal carcinomatosis. The only two cancer drugs safe to be used in such clinical settings are cytosine arabinoside (Ara-C) and methotrexate. There has been no change in this

clinical practice in the last few decades. However, with the advances in smart nanocarriers, it is likely that in the future, potent chemotherapeutic drugs or target-specific drugs encapsulated in nanocarriers can be given safely intra-theccally to the patients.

Oral administration of nanotherapeutic is possible but the nanoparticles need to be protected from gastric acidity, perhaps with enteric coated gel-caps. In addition, to simulate viral entrance through the gut epithelium, the nanoparticles need to be decorated with ligands that bind to endothelial receptors and delivered intracellularly via receptor-mediated endocytosis.

Therapeutic payload and Theranostic agents

The majority of the reported therapeutic payloads used in nanoparticle drugs are small molecule chemotherapeutic agents such as paclitaxel, doxorubicin, vincristine, and cisplatin. Small molecule target specific drugs such as tyrosine kinase inhibitors, proteasome inhibitors or m-TOR inhibitors are also feasible. Many investigators have also employed nanocarriers to deliver siRNAs and protein drugs to target tissues, but with limited success. Progress in clinical translation of cancer vaccine has been slow. Multifunctional smart nanocarrier may offer a relatively new platform for the development of cancer vaccine.

Many investigators have incorporated radiotracers into nanoparticles for whole body radioimaging [24, 25]. In conjunction with loaded conventional chemotherapy or other target-specific drugs, these radiolabeled nanoparticles can serve as theranostic agents. There is evidence that nanoparticles can be preferentially delivered to and retained at the tumor site. Conceivably, nanocarriers loaded with chemotherapeutic agents and therapeutic radionuclide such as ^{90}Yt , will allow effective treatment of metastatic cancer with combination chemoradiotherapy [26].

Conclusion

There have been rapid advances in the nanotherapeutic field in the past decade. Many smart nanocarriers have been developed, some of which have great therapeutic potential. However, there remain many challenges in translating these smart nanoparticle drugs into the clinics. Nonetheless, we believe the future of nanotherapeutics is bright, especially for reversibly crosslinked nanocarriers decorated with cancer targeting ligands that can promote endocytic uptake into the tumor cells. Such approach has potential of overcoming drug resistance that is often seen in cancers refractory to standard chemotherapies. In addition, many drugs that had failed previously because of formulation or toxicity issues may possibly be resurrected by employing smart nanocarrier for effective delivery.

References

1. Jain RK. Vascular and interstitial barriers to delivery of therapeutic agents in tumors. *Cancer Metastasis Rev.* 1990; 9(3):253–66. [PubMed: 2292138]
2. Nie S, et al. Nanotechnology applications in cancer. *Annu Rev Biomed Eng.* 2007; 9:257–88. [PubMed: 17439359]
3. Lukyanov AN, et al. Polyethylene glycol-diacyl lipid micelles demonstrate increased accumulation in subcutaneous tumors in mice. *Pharm Res.* 2002; 19(10):1424–9. [PubMed: 12425458]

4. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. *Adv Enzyme Regul.* 2001; 41:189–207. [PubMed: 11384745]
5. Fernandez-Urrusuno R, et al. Evaluation of liver toxicological effects induced by polyalkylcyanoacrylate nanoparticles. *Toxicol Appl Pharmacol.* 1995; 130(2):272–9. [PubMed: 7871540]
6. Roberts JC, Bhalgat MK, Zera RT. Preliminary biological evaluation of polyamidoamine (PAMAM) Starburst dendrimers. *J Biomed Mater Res.* 1996; 30(1):53–65. [PubMed: 8788106]
7. Rihova B, Riha I. Immunological problems of polymer-bound drugs. *Crit Rev Ther Drug Carrier Syst.* 1985; 1(4):311–74. [PubMed: 2420476]
8. Talelli M, et al. Core-crosslinked polymeric micelles with controlled release of covalently entrapped doxorubicin. *Biomaterials.* 2010; 31(30):7797–804. [PubMed: 20673684]
9. Li Y, et al. Well-defined, reversible disulfide cross-linked micelles for on-demand paclitaxel delivery. *Biomaterials.* 2011; 32(27):6633–45. [PubMed: 21658763]
10. Li Y, et al. Well-defined, reversible boronate crosslinked nanocarriers for targeted drug delivery in response to acidic pH values and cis-diols. *Angew Chem Int Ed Engl.* 2012; 51(12):2864–9. [PubMed: 22253091]
11. Rijcken CJ, et al. Hydrolysable core-crosslinked thermosensitive polymeric micelles: synthesis, characterisation and in vivo studies. *Biomaterials.* 2007; 28(36):5581–93. [PubMed: 17915312]
12. Dai J, et al. Interlayer-crosslinked micelle with partially hydrated core showing reduction and pH dual sensitivity for pinpointed intracellular drug release. *Angew Chem Int Ed Engl.* 2011; 50(40):9404–8. [PubMed: 21898731]
13. Xiao K, et al. The effect of surface charge on in vivo biodistribution of PEG-oligocholeic acid based micellar nanoparticles. *Biomaterials.* 2011; 32(13):3435–46. [PubMed: 21295849]
14. He C, et al. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. *Biomaterials.* 2010; 31(13):3657–66. [PubMed: 20138662]
15. Xiao K, et al. A self-assembling nanoparticle for paclitaxel delivery in ovarian cancer. *Biomaterials.* 2009; 30(30):6006–16. [PubMed: 19660809]
16. Xiao K, et al. PEG-oligocholeic acid telodendrimer micelles for the targeted delivery of doxorubicin to B-cell lymphoma. *J Control Release.* 2011; 155(2):272–81. [PubMed: 21787818]
17. Song S, et al. Novel peptide ligand directs liposomes toward EGF-R high-expressing cancer cells in vitro and in vivo. *FASEB J.* 2009; 23(5):1396–404. [PubMed: 19124558]
18. von Maltzahn G, et al. In vivo tumor cell targeting with “click” nanoparticles. *Bioconjug Chem.* 2008; 19(8):1570–8. [PubMed: 18611045]
19. Xiao K, et al. “OA02” peptide facilitates the precise targeting of paclitaxel-loaded micellar nanoparticles to ovarian cancer in vivo. *Cancer Res.* 2012; 72(8):2100–10. [PubMed: 22396491]
20. Matsumura Y, et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. *Br J Cancer.* 2004; 91(10):1775–81. [PubMed: 15477860]
21. Gradishar WJ, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol.* 2005; 23(31):7794–803. [PubMed: 16172456]
22. Hamaguchi T, et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Br J Cancer.* 2007; 97(2):170–6. [PubMed: 17595665]
23. *NCCN Guidelines.* 2012 version 3.2012:[Available from: <http://www.nccn.org>.]
24. Shao X, et al. 125I-labeled gold nanorods for targeted imaging of inflammation. *ACS Nano.* 2011; 5(11):8967–73. [PubMed: 22003968]
25. Huang X, et al. Long-term multimodal imaging of tumor draining sentinel lymph nodes using mesoporous silica-based nanoprobes. *Biomaterials.* 2012; 33(17):4370–8. [PubMed: 22425023]
26. Wang AZ, et al. ChemoRad nanoparticles: a novel multifunctional nanoparticle platform for targeted delivery of concurrent chemoradiation. *Nanomedicine (Lond).* 2010; 5(3):361–8. [PubMed: 20394530]