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Image-guided interventional therapy for cancer with radiotherapeutic nanoparticles ☆

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ABSTRACT

One of the major limitations of current cancer therapy is the inability to deliver tumoricidal agents throughout the entire tumor mass using traditional intravenous administration. Nanoparticles carrying beta-emitting therapeutic radionuclides that are delivered using advanced image-guidance have significant potential to improve solid tumor therapy. The use of image-guidance in combination with nanoparticle carriers can improve the delivery of localized radiation to tumors. Nanoparticles labeled with certain beta-emitting radionuclides are intrinsically theranostic agents that can provide information regarding distribution and regional dosimetry within the tumor and the body. Image-guided thermal therapy results in increased uptake of intravenous nanoparticles within tumors, improving therapy. In addition, nanoparticles are ideal carriers for direct intratumoral infusion of beta-emitting radionuclides by convection enhanced delivery, permitting the delivery localized therapeutic radiation without the requirement of the radionuclide exiting from the nanoparticle. With this approach, very high doses of radiation can be delivered to solid tumors while sparing normal organs. Recent technological developments in image-guidance, convection enhanced delivery and newly developed nanoparticles carrying beta-emitting radionuclides will be reviewed. Examples will be shown describing how this new approach has promise for the treatment of brain, head and neck, and other types of solid tumors.

Contents

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1. Introduction

1.1. Challenges in drug targeting and delivery to solid tumors of intravenously administered drugs

One of the major challenges of current cancer therapy is the inability to deliver intravenously administered tumoricidal drugs throughout the solid tumor mass. One reason for this is that intravenously administered drugs are inhibited in their intratumoral penetration by high interstitial pressures which prevent diffusion of drugs from the blood circulation into the tumor tissue [1–5]. This problem is compounded by the relatively rapid clearance of intravenously administered drugs from the blood circulation by kidneys and liver. In addition, drugs that do reach the solid tumor by diffusion are inhomogeneously distributed at the micro-scale. This problem of inadequate intratumoral drug levels cannot be overcome by simply administering larger systemic doses as toxicity to normal organs is generally the dose limiting factor. The use of nanoparticles for carrying anti-cancer drugs is one method for increasing the drug accumulation in tumor following intravenous administration since the nanoparticles can be passively targeted and accumulate in the tumor through the enhanced permeability and retention (EPR) effect [6–8]. However, even nanoparticulate drugs have poor penetration from the vascular compartment into the tumor and the nanoparticles that do penetrate are most often heterogeneously distributed [9–11]. Imaging methods at the micro-scale are being developed to better understand the heterogeneous pattern of nanoparticle accumulation in an attempt to develop new therapies [12–14].

1.2. Inclusion of imaging in drug delivery studies

Imaging is becoming an integral component of drug development as well as for monitoring drug delivery and the response of targeted processes to the therapy [15–17]. Imaging can be used to guide minimally invasive procedures such as guiding a needle for tumor biopsy which is much less invasive than collecting specific tumor samples surgically [18]. Companion imaging probes targeting molecular features determined from the biopsy sample can be integrated into the drug development process. In addition, the inclusion of a companion imaging probe during drug development can aid in determining the clearance kinetics and tissue distribution of the drug non-invasively using imaging modalities such as single photon emission computed tomography (SPECT), positron emission tomography (PET), X-ray computed tomography (CT), magnetic resonance imaging (MRI), ultrasound or optical methods [19]. This companion imaging probe can also be used to determine the likelihood of the drug reaching the tumor and to what extent. In this situation of personalized medicine, individual cancer patients can be stratified for promising drug treatment responses with this type of imaging. Drugs that have increased accumulation within the targeted site are likely to be more effective as compared with others with minimal accumulation at the target site [19]. This makes treatment more efficient and cost effective. Moreover, the Food and Drug Administration requires the availability of a companion diagnostic test to select patients for targeted therapies and in many cases this diagnostic is an imaging agent [20,21].

Nanoparticle-based drugs have an additional advantage over free drugs with their potential to be multifunctional carriers capable of carrying both therapeutic and diagnostic imaging probes (theranostic) in the same nanocarrier. These multifunctional nanoparticles can serve as theranostic agents and facilitate personalized treatment planning. Additionally, nanoparticles are less likely to be affected by inclusion of an imaging component within their structure unlike small molecule, peptide, oligonucleotide and proteins (monoclonal antibodies) which can more readily lose functionality by the addition of imaging probes. The design and testing of potential theranostic nanoparticles has been a burgeoning area of research in the past 15 years. An exhaustive review of these nanoparticle constructs is outside of the scope of this article and previous review articles covering this topic are available in the literature [16,22–29].

1.3. Image-guidance for enhancing drug delivery of intravenously administered nanoparticle-based drugs

Imaging can also be used for localization of the tumor to improve the placement of a catheter or external device within tumors to cause cell

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