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Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Image-guided interventional therapy for cancer with radiotherapeutic nanoparticles[☆]

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ARTICLE INFO

Article history:

Accepted 1 July 2014

Available online xxxx

Q2 Keywords:

Radionuclide therapy

Convection enhanced delivery

Imaging

Solid tumor

Liposomes

Rhenium-186

Drug delivery

Radiofrequency ablation

Beta-emitting radionuclides

Image guidance

High intensity focused ultrasound

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.

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Contents

1.	Introduction	0
1.1.	Challenges in drug targeting and delivery to solid tumors of intravenously administered drugs	0
1.2.	Inclusion of imaging in drug delivery studies	0
1.3.	Image-guidance for enhancing drug delivery of intravenously administered nanoparticle-based drugs	0
1.4.	Radiotherapeutic nanoparticles	0
1.5.	Ideal theranostic properties of certain beta-emitting radionuclides	0
2.	Image-guidance for thermal ablation combined with intravenous nanoparticles	0
2.1.	Radiofrequency ablation combined with chemotherapeutic nanoparticles	0
2.2.	Radiofrequency ablation combined with radiotherapeutic nanoparticles	0
2.3.	High intensity focused ultrasound combined with nanoparticle therapeutics	0
3.	Intratumoral administration of nanoparticle drugs	0
3.1.	Convection enhanced drug delivery	0
3.2.	CED nanoparticle therapeutic as possible adjuvant therapy	0
3.3.	CED challenges	0
3.4.	Advantages of using β -emitting radionuclides with intratumoral CED nanoparticle therapy	0
3.5.	Recent technological progress in image-guidance	0

[☆] This review is part of the Advanced Drug Delivery Reviews theme issue on "Targeted Imaging".

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60	4.	Advantages of nanoparticles for intratumoral CED administration	0
61	4.1.	Nanoparticles have improved retention within the tumor	0
62	4.2.	Nanoparticles have excellent dispersion through the tumor with CED administration	0
63	5.	History of intratumorally administered radiotherapeutic nanoparticles	0
64	5.1.	Liposomes	0
65	5.1.1.	Head and neck cancer	0
66	5.1.2.	Glioblastoma	0
67	5.2.	Solid lipid nanocapsules	0
68	5.3.	Radioactive gold nanoparticles	0
69	5.4.	Metallofullerene nanoparticles radiolabeled with lutetium-177 (¹⁷⁷ Lu)	0
70	6.	Future directions for image-guided nanoparticle therapy	0
71	6.1.	Development of methods to improve CED coverage of and retention within a solid tumor	0
72	6.1.1.	Improvement in catheter design	0
73	6.1.2.	Use of non-invasive image guidance to improve solid tumor coverage	0
74	6.2.	Further investigations into the ideal characteristics of nanoparticles for CED for enhanced volume of distribution and tumor retention	0
75	6.2.1.	Investigations of the most ideal size of nanoparticles for CED administration	0
76	6.2.2.	Multifunctional nanoparticles for tracking CED distribution within tumors	0
77	6.3.	Therapeutic ultrasound to enhance the convection of intratumoral nanoparticles	0
78	6.4.	Investigations into different β -emitting radionuclides for intratumoral image-guided therapy	0
79	6.5.	Nanoparticles as ideal carriers to target intratumoral macrophages/microglia	0
80	6.5.1.	Macrophage/microglia in glioblastoma tumor	0
81	6.5.2.	Macrophages/microglia as intratumoral transporters of nanoparticles	0
82	6.6.	Potential for combination of chemotherapy with radionuclide nanoparticle therapy, i.e. chemo-radionuclide therapy	0
83	6.7.	Potential for immunostimulation of radiotherapeutic nanoparticles	0
84	7.	Conclusions	0
85		Acknowledgments	0
86		References	0

87

88 1. Introduction

89 1.1. Challenges in drug targeting and delivery to solid tumors of intravenously 90 administered drugs

91 One of the major challenges of current cancer therapy is the inability
92 to deliver intravenously administered tumoricidal drugs throughout the
93 solid tumor mass. One reason for this is that intravenously administered
94 drugs are inhibited in their intratumoral penetration by high interstitial
95 pressures which prevent diffusion of drugs from the blood circulation
96 into the tumor tissue [1–5]. This problem is compounded by the rela-
97 tively rapid clearance of intravenously administered drugs from the
98 blood circulation by kidneys and liver. In addition, drugs that do reach
99 the solid tumor by diffusion are inhomogeneously distributed at the
100 micro-scale. This problem of inadequate intratumoral drug levels
101 cannot be overcome by simply administering larger systemic doses as
102 toxicity to normal organs is generally the dose limiting factor. The use
103 of nanoparticles for carrying anti-cancer drugs is one method for
104 increasing the drug accumulation in tumor following intravenous ad-
105 ministration since the nanoparticles can be passively targeted and accu-
106 mulate in the tumor through the enhanced permeability and retention
107 (EPR) effect [6–8]. However, even nanoparticulate drugs have poor pen-
108 etration from the vascular compartment into the tumor and the nano-
109 particles that do penetrate are most often heterogeneously distributed
110 [9–11]. Imaging methods at the micro-scale are being developed to bet-
111 ter understand the heterogeneous pattern of nanoparticle accumulation
112 in an attempt to develop new therapies [12–14].

113 1.2. Inclusion of imaging in drug delivery studies

114 Imaging is becoming an integral component of drug development as
115 well as for monitoring drug delivery and the response of targeted pro-
116 cesses to the therapy [15–17]. Imaging can be used to guide minimally
117 invasive procedures such as guiding a needle for tumor biopsy which
118 is much less invasive than collecting specific tumor samples surgically
119 [18]. Companion imaging probes targeting molecular features deter-
120 mined from the biopsy sample can be integrated into the drug

development process. In addition, the inclusion of a companion imaging 121
probe during drug development can aid in determining the clearance 122
kinetics and tissue distribution of the drug non-invasively using imag- 123
ing modalities such as single photon emission computed tomography 124
(SPECT), positron emission tomography (PET), X-ray computed tomog- 125
raphy (CT), magnetic resonance imaging (MRI), ultrasound or optical 126
methods [19]. This companion imaging probe can also be used to deter- 127
mine the likelihood of the drug reaching the tumor and to what extent. 128
In this situation of personalized medicine, individual cancer patients 129
can be stratified for promising drug treatment responses with this 130
type of imaging. Drugs that have increased accumulation within the 131
targeted site are likely to be more effective as compared with others 132
with minimal accumulation at the target site [19]. This makes treatment 133
more efficient and cost effective. Moreover, the Food and Drug Admin- 134
istration requires the availability of a companion diagnostic test to se- 135
lect patients for targeted therapies and in many cases this diagnostic 136
is an imaging agent [20,21]. 137

Nanoparticle-based drugs have an additional advantage over free 138
drugs with their potential to be multifunctional carriers capable of car- 139
rying both therapeutic and diagnostic imaging probes (theranostic) in 140
the same nanocarrier. These multifunctional nanoparticles can serve 141
as theranostic agents and facilitate personalized treatment planning. 142
Additionally, nanoparticles are less likely to be affected by inclusion of 143
an imaging component within their structure unlike small molecule, 144
peptide, oligonucleotide and proteins (monoclonal antibodies) which 145
can more readily lose functionality by the addition of imaging probes. 146
The design and testing of potential theranostic nanoparticles has been 147
a burgeoning area of research in the past 15 years. An exhaustive review 148
of these nanoparticle constructs is outside of the scope of this article and 149
previous review articles covering this topic are available in the literature 150
[16,22–29]. 151

152 1.3. Image-guidance for enhancing drug delivery of intravenously 153 administered nanoparticle-based drugs

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

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