Advanced Drug Delivery Reviews 65 (2013) 2045–2060

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Carbon nanotubes in hyperthermia therapy ☆

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ARTICLE INFO

Article history:
Accepted 1 August 2013
Available online 8 August 2013

Keywords:
Photothermal therapy
Carbon nanotubes
Single-walled nanotubes
Multiwalled nanotubes
Cancer therapy

ABSTRACT

Thermal tumor ablation therapies are being developed with a variety of nanomaterials, including single- and multiwalled carbon nanotubes. Carbon nanotubes (CNTs) have attracted interest due to their potential for simultaneous imaging and therapy. In this review, we highlight in vivo applications of carbon nanotube-mediated thermal therapy (CNMTT) and examine the rationale for use of this treatment in recurrent tumors or those resistant to conventional cancer therapies. Additionally, we discuss strategies to localize and enhance the cancer selectivity of this treatment and briefly examine issues relating the toxicity and long term fate of CNTs.

Contents

1. Introduction

Carbon nanotubes (CNTs) consist of one or more seamless, cylindrical graphitic sheets of sp2 carbon atoms bonded together in an edgeless, hexagonal network [1]. Their combination of electrical, thermal and spectroscopic properties has evoked great interest; biomedical researchers are using CNTs to develop new technologies for the detection, monitoring and therapy of diseases including cancer [2–6]. CNTs can be internalized easily by cells [7–9] and act as delivery vehicles for drugs, nucleic acids, and imaging agents [7,10–23]. Their unique optical, thermal and cancer selective properties afford the possibility to engineer multiple diagnostic and therapeutic functions into a single particle [2,24]. This makes CNTs extremely suitable for further biomedical development [25].

Minimally invasive, rapidly administered, and highly selective nanotechnology-based thermal tumor ablation therapies are being developed with a variety of nanomaterials (reviewed in [26]). These include single walled carbon nanotubes (SWCNTs) [27], multiwalled carbon nanotubes (MWCNTs) [28], graphene [29], iron

☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "Carbon nanotubes in medicine and biology — Therapy and diagnostics".

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http://dx.doi.org/10.1016/j.addr.2013.08.001

oxide nanoparticles [30], gold nanorods [31] and gold nanoshells [32,33]. Heat-based cancer therapy requires elevation of malignant tissues to supraphysiologic temperatures [34–39]. Exposure to high temperature for a sufficient amount of time causes physical damage such as protein denaturation and membrane lysis and can increase oxidative stress [34,35,40,41]. These effects may be cytotoxic on their own, causing coagulative necrosis or apoptosis [37,39]. Additionally, hyperthermic treatments that increase temperatures more modestly may enhance the anti-cancer efficacy of ionizing radiation or systemic chemotherapy regimens [40,42,43].

Dose limiting toxicities resulting from diffuse heating of non-tumor tissues and the relative invasiveness of thermal ablative instrumentation have limited wider clinical use of thermal ablation for cancer therapy [44]. However, with recent refinements in technology, the role of such therapies should increase in the near future [26,45,46], and nanotechnology is playing a key role in these advances. Human clinical trials are ongoing for a gold nanoshell based photothermal cancer therapy (Id: NCT00848042 on ClinicalTrials.gov) and for iron oxide nanoparticle-based magnetic thermotherapy [47,48]. Although the results of these studies are promising, there remains significant room to improve upon both the generation and localization of heat for thermal therapy.

In this arena, CNTs have emerged as promising, next generation agents for thermotherapy of cancer. Currently, significant efforts are being applied to develop CNT-based, clinical treatments. In this review, we will specifically high-light in vivo applications of CNT-mediated thermal therapy (CNMTT) and examine the rationale for use of this treatment in recurrent tumors or those resistant to conventional cancer therapies. Additionally, we will identify strategies to localize and enhance the cancer selectivity of this treatment, and briefly examine issues relating the toxicity and long term fate of CNTs.

2. CNT-mediated thermal therapy: rationale and current status

Carbon nanotubes offer an exceptional combination of attributes for the development of the next generation of photothermal agents; chief among these is their ability to efficiently convert near infrared radiation (NIR) into heat [49]. Compared to other wavelengths of light, the transmission of NIR through the body is poorly attenuated by biological systems [50,51]. Penetration of light through tissue is fundamental to photothermal applications of nanomaterials for the treatment of non-superficial cancerous lesions in vivo [28]. Following exposure to NIR, CNTs enter an excited state and release vibrational energy that is transformed into heat, which can induce cell death [27,52].

CNTs possess an extremely broad electromagnetic absorbance spectrum, covering the full spectra of both the NIR I and II windows [53], which correspond to the “optical transmission window” of biological tissues [50,51], and the radio frequency and microwave bands as well [54]. Further tuning of the photophysical properties of CNTs can be achieved by tailoring the wall number, diameter, and length of the nanotubes according to the “nano-attenna” effect [52]. Critically, NIR absorption and energy transduction efficiency remains high across a wide frequency range [53], which allows for flexibility in the choice of both material characteristics (diameters from <2 nm to >30 nm; lengths from <100 nm to > 1 μm) and excitation wavelengths. This provides great versatility to tailor size, shape, and surface properties to optimize the tissue distribution of CNTs without a significant loss in thermal conversion efficiency. The broad electromagnetic absorbance spectrum of CNTs also offers a significant advantage over plasmonically heated nanomaterials (such as gold nanoshells and nanorods) for which the excitation spectra are highly dependent upon the size and shape of the particles [2]. While direct comparisons are difficult to make, some estimates indicate that CNTs can achieve thermal destruction of tumors at 10-fold-lower doses and 3-fold-lower power than is needed for gold nanorods [53]. However, in contrast to gold nanoparticles, which can be synthesized with great uniformity and have already been tested in human clinical trials, production of uniform, well-characterized CNTs remains a significant hurdle for clinical translation.

CNTs exhibit both advantages and limitations in thermal therapy when compared to iron oxide nanoparticles. The magnetic field used to excite iron oxide nanoparticles as a means of generating heat offers superior depth of energy penetration as compared to NIR, but the slower rate of heating induced by this technique leads to significant thermal diffusion away from the targeted area (discussed in Section 2.3), potentially increasing collateral damage to neighboring healthy tissue [55]. A second drawback of this technique is that it also requires the removal of all metallic materials within the magnetic field covering the treatment area including dental fillings, crowns and implants. On the other hand, iron oxide nanoparticles, like gold nanoparticles, share a significant advantage over CNTs because uniform preparations of iron-based nanoparticles can be synthesized and have already been tested in human clinical trials.

In most cases, the clinical model for the use of CNTs as heat transduction agents is based upon laser-induced thermotherapy (LITT) [33,39], a photothermal ablation technique in which an NIR laser is used to heat a target tissue, such as a tumor, above the thermal ablation temperature threshold of approximately 55 °C [33,56]. A major limitation of LITT has been an inability to consistently achieve thermoablative temperatures throughout the target lesion and to confine treatment exclusively to the tumor [57,58]. Therefore, to be of clinical benefit, CNTs must greatly improve the deposition of heat following NIR exposure without causing any significant toxicity on their own.

2.1. In vivo anticancer efficacy of CNT-mediated thermal therapy

The efficacy of CNMTT for the treatment of locoregional tumors in vivo has been demonstrated using syngeneic models of cancer in mice [53,59], rabbits [54], and in human xenografts grown in mice (reviewed in [49]). In most cases, CNTs are injected systemically or directly into the tumor, which is then exposed to an external NIR (typically a YAG or diode laser) or microwave source. As highlighted in Table 1, CNMTT has proven effective for the treatment of a wide variety of cancer types both in vitro and in vivo. In this review, we will focus our discussion upon recent developments in CNMTT treatment of human cancer xenografts in animal models.

Initial in vivo studies of CNMTT focused on the use of SWCNTs, and the results were mixed. Moon et al. demonstrated that following intratumoral injection of SWCNTs into mice bearing flank xenografts of human mouth carcinoma cells and NIR irradiation (3 W/cm^2; 3 min), the tumors were completely destroyed [60]. Normal tissue adjacent to the treated area was spared; however, the irradiation procedure itself resulted in significant burning of the heated area even in the absence of SWCNTs. Significantly, no indication of tumor recurrence or apparent side effects of treatment were observed during several months of follow-up [60]. Huang et al. achieved more modest results following a similar treatment [59]. Using mice bearing syngeneic murine squamous cell tumors, the researchers intratumorally injected SWCNTs and irradiated the tumor with a low power (200 mW/cm^2) NIR laser for 10 min. They observed that treatment resulted in a maximum tumor temperature of approximately 55 °C, indicating that the thermal ablation threshold was reached. However, while a reduction in tumor growth and a modest survival advantage were documented, this treatment failed to achieve a durable cancer remission. In contrast to Moon et al. [60], necrotic normal tissue was present adjacent to the treatment site, indicating significant heat transfer away from the targeted site and into the surrounding non-tumor region. As discussed in more detail in Section 2.3, recent work by Xie et al. [61] modeling the effects of energy deposition rate on the efficacy of CNMTT suggest that the slower rate of energy deposition used by Huang et al. [59] as compared to Moon et al. [60] may have resulted in greater heat diffusion leading to lesser treatment efficacy and more collateral damage to surrounding tissue.