Clinical Oncology xxx (2013) 1–11

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Radiosensitising Nanoparticles as Novel Cancer Therapeutics — Pipe Dream or Realistic Prospect?

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Received 27 February 2013; received in revised form 1 May 2013; accepted 27 June 2013

Abstract

The field of high atomic number nanoparticle radiosensitising agents is reviewed. After a brief discussion of the new mode of physicochemical action implied by irradiation of high atomic number nanoparticles embedded in biological systems, a series of exemplars are discussed. Silver-, gadolinium- and gold-based nanoparticles are discussed in order of increasing atomic number with functionalisation strategies being outlined. *In vitro* and *in vivo* evidence for radio-enhancement and the mechanisms attributed to the increased biological effect are discussed.

Key words: Cancer; nanoparticles; nanotechnology; radiation dose enhancement

Statement of Search Strategies Used and Sources of Information

The review was based on Medline, Google Scholar and PubMed searches of key influential literature and the most recent advances (2010–present). Specific search terms included nanotechnology, nanoparticles, radiosensitisation, dose enhancement, silver, gadolinium, gold, preclinical and clinical trials.

Introduction

An interdisciplinary approach to the development of future therapeutics has helped fuel the nanoscale revolution of the past decade. This has led to the production of a multiple of nanoparticle preparations for the treatment of a variety of pathological conditions, ranging from novel scaffolds for tissue engineering to new HIV therapeutics and perhaps most commonly for the development of new anticancer agents [1,2,3,4]. This review specifically details various nanoparticle preparations that have been created to augment the efficacy of current radiotherapy treatment plans.

By far the most common radiosensitising approach is to exploit the increased photon absorption of high atomic number (Z) materials at kilovoltage (kVp) photon energies [5]. Adopting this approach, therapeutic nanoparticles have been produced using silver ($Z = 47$), gadolinium ($Z = 64$) and most extensively gold ($Z = 79$). In addition to the high atomic number of these materials, the unique physicochemical properties of these nanomaterials permit relatively simplistic functionalisation through the binding of amine and thiol subgroups [6]. Furthermore, increasingly complex multifunctionalisation strategies have resulted in new terminology, such as theranostics, where a particle is designed for both therapeutic and diagnostic purposes [7,8].

Physicochemical Mode of Action

In contrast to the low atomic number species found predominantly in living systems, the presence of the high Z species interacting with highly ionising radiation implies a new physicochemical mode of action. Due to the

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.06.011

Please cite this article in press as: Coulter JA, et al., Radiosensitising Nanoparticles as Novel Cancer Therapeutics — Pipe Dream or Realistic Prospect? Clinical Oncology (2013), http://dx.doi.org/10.1016/j.clon.2013.06.011

photoelectric effect, these high atomic number species can undergo inner-shell ionisation, where one of the deeply bound electrons is removed, with high efficiency. The result is a highly unstable atomic system that stabilises by emission of lower energy photons (fluorescence) and electrons (Auger emission). Several Auger emissions can occur effectively simultaneously from a single inner shell ionisation in a process called an Auger cascade. The electrons produced by this Auger cascade typically have energies of a few keV or less and, hence, they have penetrations of typically 10–100 nm [9]. As a result, these electrons deposit their energy very locally. This highly localised deposition of energy is akin to that found in ion therapy and indeed the biological effect has been well described using the local effect model first developed to relate ion-induced radiation track structure to biological effect [10,11]. This highly localised deposition of energy is one of the attractive features of nanoparticles clinically — if appropriately localised, they offer the promise of performance usually associated only with heavy ion facilities but using conventional clinical linacs. However, a full description of the mode of action following from the localised energy deposition brought about through the Auger cascade is still not available. For example, the energy dependence for DNA damage by gold nanoparticles in the photon energy range (20–80 keV) shows an unexplained double maximum [12]. This is significant because this energy range is the range over which photoelectric interactions with gold nanoparticles (e.g. from shower particles) are most likely. This unexplained energy dependence in even such a simple system shows the difficulty in connecting this collective physical mode of action, via physicochemical processes to biological effects. The physical basis of radiosensitisation and the resultant biological mechanisms have been reviewed elsewhere, for the specific case of gold nanoparticles [13].

Silver Nanoparticles ($Z = 47$)

Zhao *et al.* [14] developed a multifunctional magnetic iron/silver nanocomposite particle functionalised with cetuximab, a monoclonal antibody designed to target the epidermal growth factor receptor (EGFR). This is an attractive target as up-regulation of EGFR is commonly observed in many cancers, including nasopharyngeal carcinomas, and is strongly associated with tumour metastasis, recurrence and poor overall survival [15,16]. The Fe(3)O(4)/Ag–cetuximab nanoparticle evoked dose-dependent cytotoxicity with an IC_{50} concentration of 350 ± 3.14 μg/l. However, when used in combination with radiation at 30 μg/l (about 10% of the IC_{50} concentration), significant radiosensitisation was achieved, producing an impressive dose enhancement factor (DEF) of 2.26. In addition to high Z radiosensitation caused by the silver nanoparticles, additional functionality was conferred by the conjugation of cetuximab, resulting in the attenuation of EGFR by about 50% [14]. This reduction is particularly relevant as EGFR signalling through downstream pathways such as Ras-mitogen-activated protein kinase, phosphatidyl inositol 3-kinase-Akt and Jak-STAT have been associated with solid tumour radioresistance [17,18]. An earlier study investigating silver nanoparticles as sensitisers for the treatment of radioresistant glioblastoma tumours reported variable efficacy dependent upon nanoparticle size and concentration [19]. The extent of the sensitising capability was further enhanced using higher concentrations of the nanoparticles, while maximising the surface area to volume ratio by opting for smaller-sized particles. In this instance, the authors proposed that the mode of sensitisation was due to the release of Ag^+ cations, which subsequently captured free electrons, generating an oxidative agent, which further reduced ATP production and increased the production of intercellular reactive oxygen species (ROS) [20]. In addition to enhancing the generation of potentially damaging radicals, silver nanoparticles have also been shown to negatively regulate the activity of DNA-dependent protein kinase, a key enzyme involved in DNA damage repair via non-homologous end joining [21]. This finding is particularly relevant, as the primary mode of radiation-induced cytotoxicity is the generation of potentially lethal double-strand breaks (DSB). Therefore, novel therapeutics that augment the radiation-induced damage profile while inhibiting the repair process have attracted much attention [22,23].

Gadolinium Nanoparticles ($Z = 64$)

Other high Z materials, such as gadolinium, have been investigated on the nanoscale as potential radiosensitising agents. Le Duc *et al.* [24] developed a 2 nm gadolinium nanoparticle as a positive contrast agent to enhance magnetic resonance imaging and as a novel radiosensitiser. A rat intracerebral 9 L gliosarcoma model was chosen to show the theranostic properties of this nanoparticle preparation. The authors described both preferential accumulation within the tumours, attributed to the enhanced permeability and retention effect (EPR) caused by the tortuous and leaky tumour vasculature and an increased radiosensitising capacity [24,25,26]. This effect was neatly shown by the difference in clearance rates between the two hemispheres of the brain. In the normal left hemisphere of the rat brain, the gadolinium nanoparticle signal increased for up to 5 min, after which point the intracerebral concentration rapidly decreased by about 53%, 20 min after administration of the nanoparticles. However, in the right hemisphere and in particular within the 9 L gliosarcoma, gadolinium nanoparticles were retained and cleared much slower with 88% of the maximal gadolinium nanoparticles retained 20 min after administration [24] (Figure 1). On this occasion, image-guided microbeam (~25–100 μm) radiation therapy, designed to spare normal brain tissue, was administered, using the positive magnetic resonance imaging signal conferred by the gadolinium nanoparticles as a treatment delivery guide. Due to the extremely aggressive and invasive nature of gliosarcoma tumours, the median survival time for untreated animals was 19 days. This was significantly improved upon with the administration of microbeam radiation therapy, extending the median survival time to 47 days, an increase in survival time by 147%. However,

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