Cancer Letters ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Nanoparticles in radiation oncology: From bench-side to bedside

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ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 7 March 2016
Accepted 8 March 2016

Keywords:
Nanoparticles
Radiotherapy
Radio-sensitizer
Drug vector
Clinical trials

ABSTRACT

Nanoparticles (NP) are "in vogue" in medical research. Pre-clinical studies accumulate evidence of NP enhancing radiation therapy. On one hand, NP, selected for their intrinsic physicochemical characteristics, are radio-sensitizers. Thus, when NP accumulate in cancer cells, they increase the radiation absorption coefficient specifically in tumour tissue, sparing healthy surrounding tissue from toxicity. On the other hand, NP, by being drug vectors, can carry radio-sensitizer therapeutics to cancer cells. Finally, NP present theranostic effects. Indeed they are used in imaging as contrast agents. NP therefore can be multi-tasking and have promising prospect in radiotherapy field.

In spite of the numerous encouraging preclinical evidence, the very small number of clinical trials investigating NP possible involvement in the radiotherapy clinical practice suggests a physicians' unwillingness. Many prerequisites seem necessary including define biological mechanisms of NP radiosensitization pathways and of NP clearance. NP biocompatibility and toxicities should be better investigated to select, among the extensive range of possible systems, the harmless and most efficient one, and to finally come to a safe and successful clinical use. The present review focuses on the various interests of NP in the radiotherapy area and proposes a discussion about their role in the future clinical practice.

Introduction

Radiation therapy is one of the main cancer treatment strategies. Nowadays, radiotherapy has significant challenges to enhance its efficacy by increasing doses while reducing damage to surrounding tissues. Two strategies can then be considered: to radio-protect the healthy surrounding tissue (using amifostine, antioxidants, phytochemicals, etc.) and to radio-sensitize the tumour tissue. Over the past few years there has been a considerable increase in interest in the use of formulations using nanoparticles (NP) [1,2].

According to the ISO International Standards, NP are defined as particles which do not exceed 100 nm in their three dimensions. The use of NP designs a new landscape in the era of modern oncology and offers new perspectives for diagnosis as well as therapeutics. Depending on their specific physicochemical properties, NP present three main applications in the oncology landscape [3]: medical imaging, drug vectorization and radiation-sensitization. For the imaging area, their super-paramagnetic effects are used in MRI. For medical oncology and pharmacology, they present a particular bio-distribution and pharmacokinetic, and can be used to target the drugs' destination. The enhancement of the radio-sensitizer effect is also a promising aspect of this technology. The concept is to increase tumour absorption capacity through the incorporation of NP and thus increase, very focally, the dose delivered by the particle beams. Consequently, the differential effect between normal and tumour tissues is improved [4].

The aim of the present study was to describe the place of the nanoparticles in all fields of radiation oncology, from pre-clinical models to early phase clinical trials aimed at proving this concept.

Tumour targeting

The use of tumour site targeted radio-sensitizers could improve the therapeutic window. Indeed, it leads to a higher radio-sensibility of cancer cells compared to healthy ones. Thanks to their physical properties, NP have the ability to penetrate preferentially in tumour tissues. The enhanced permeability and the retention effect refer to the preferential accumulation of NP within the tumours because

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http://dx.doi.org/10.1016/j.canlet.2016.03.011
0304-3835/

of the greater porosity of tumour neo-vessels [5]. Indeed, solid tumours are characterized by an important and fenestrated vasculature which is associated, in addition, with a poor lymphatic drainage. These characteristics induce an EPR (Enhanced Permeation and Retention) effect, responsible for NP's targeting and accumulation in tumours [6]. However this "passive" targeting is jeopardized [7] by NP rapid uptake in liver and spleen [8] upon intravenous (*i.v.*) route, which reduce their uptake in the tumour.

Tumour targeting can be improved by coupling NP to tumour specific antibodies or ligands [9]. Even if some results are contradictory, it seems that a NP coating with targeted antibody may facilitate tumour cell internalization of NP via a receptor-mediated endocytosis. As an example, a Canadian group synthetized a Human Epidermal Growth Factor Receptor-2 (HER2)-targeted gold NP (GNP) by conjugating trastuzumab (Herceptin) to 30 nm GNP [10]. HER-2 can be over-expressed at the surface of some breast cancer cells. The authors described, at both, *in vitro and in vivo* levels, the NP accumulation in the tumour cells and their radio-sensitizer effect. Other gold nano-probes, presenting a high specificity for αvβ3 integrin positive cells, showed a pretty good accumulation in tumour site, as described by MRI [11].

Another way to target efficiently the site is to administrate the intra-tumour (*i.t.*). Assessing the HER2-GNP formulation described above, the authors describe that *i.t.* is more efficient for GNP uptake within the tumour than *i.v.* injection. Surprisingly they describe that HER-2-GNP administrated in *i.v.* route were more extensively sequestered by liver and spleen than non-targeted GNP, which circulated longer, allowing higher tumour uptake [12].

Moreover, NP are cleaned by the immune system. In order to prolong their effect, a polyethylene glycol (PEG) coating could be required [13]. However a compromise must be done during the NP design because the radio-sensitizer effect requires a minimal coating.

Intrinsic radio-sensitizer power of a nano-technology

Physical aspect

It has been reported a long time ago that the biological effects of a localized irradiation were increased in the presence of high Z material nearby the irradiated targeted volume. The densely packed metal particles can selectively scatter and/or absorb the high energy radiations. From a biological point of view, it was observed that there were increased chromosomal damages in lymphocytes of patients undergoing iodine injection for angiography [14]. High-Z atoms interact with ionizing radiations by producing secondary particles: diffused photons, photoelectrons, Auger electrons, Compton electrons, and fluorescence photons [1]. For low energy photons (<60 keV), there is a pre-eminence of the photoelectric effect: all the energy of the incident photon is transferred to an electron from an internal atomic orbital which is ejected. Then, an electronic shell rearrangement leads to the emission of a fluorescence photon or an Auger electron. The fluorescence photons have a low attenuation. The Auger electrons generate a focal ionization of high-density in the neighbouring tissue, on a distance of almost 10 nm. The energy that is produced by photoelectric effect depends on the atomic number (Z) [15] and on the incident photon energy (E), according to the $(Z/E)^3$ ratio.

For higher energies, the main interaction is an inelastic diffusion, also called Compton effect: a high-energy incident photon ejects an electron from the peripheral atomic shell, which diffuses with a lower energy. When energies are still increased (>MeV, which is the energy range used in radiation therapy), there is a pair production: the energy of the incident photon is totally transferred to an electron and a positron. This effect varies with Z^2. Thus, the differential between gold atoms (Z = 79) and water molecules (Z = 7.4) is much lower for MeV energies than with keV photons producing a photoelectric effect. Consequently, most of the available pre-clinical studies combining NP and radiation therapy have used keV photons to take the optimal advantage of the photoelectric effect. However, this energy range is not relevant for therapeutics (with the noticeable exceptions of brachytherapy and contact therapy).

Biological aspect

In parallel with this "physical" interaction characterized by a secondary diffusion of energy on metallic particles' surface which induces an increase of DNA damages, some studies suggest the implication of biological pathways.

Indeed, few studies demonstrated an increase of apoptosis [16–18], necrosis [19,20] and autophagy [21] when irradiated cells were in contact with NP. *In vivo*, histological observation and immunohistochemical analysis have been carried out to illustrate the same conclusion about increased apoptosis occurrence [22,23]. The mechanisms involved in the generation of reactive oxygen species (ROS) upon X-rays in the presence of NP sound a particularly interesting path. The GNP-induced enhancement of ·OH and $O_2^{\cdot -}$ generation was confirmed [24]. Oxidative stress is induced by NP and the endogenous ROS production is associated with NP's cytotoxicity [20,25–28]. Another biological effect has brought up in a recent study. The authors have described that their tumour targeted-GNP induced catastrophic vascular damage at the tumour site during radiation therapy. This NP vascular effect is associated with a higher cytotoxicity [29]. The impact of NP on the cell-cycle has been described as another possible pathway of NP radio-sensitizer effect [30]. Many experiments have compared the radiation-induced DNA damages in the presence or absence of NP. Most of the time, studies measure the number of DNA double-strand breaks because these DNA lesions are particularly lethal. Thus, the authors described high number of DNA damage when radiations are associated with NP [10,31–34].

If it seems clear that these biological effects act in addition to the physical properties of NP and thus highly participate to their radio-sensitizer power, biological mechanisms remain unclear and should be investigated in the next few years.

Nanos' team

Gold nanoparticles (GNP)

GNP have been the most studied NP because of their many advantages: high bio-compatibility, high penetration within the tumour and low clearance. GNP preferentially accumulate in tumours and are easily quantifiable for pharmacokinetics analyses. Numerous studies have described that GNP increase DNA damages and therefore the anti-tumour effects of ionizing radiations. A Monte Carlo-based model has been generated to predict the GNP radio-sensitizer effect [35]. Because classical dosimetry is not applicable to NP-enhanced radiation therapy, new methods have been recently developed [36]. An interesting study in a murine model of glioblastoma xeno-grafts suggested that radiations induce a modulation of the blood–brain barrier leading to an increased uptake of GNP. Thus, the accumulation of GNP in the cerebral tumour site could improve the radiation benefits on overall survival [37].

Gadolinium nanoparticles (GBN)

Gadolinium is nowadays a NP of interest, especially because it has the particularity to be easily viewed through magnetic resonance

Please cite this article in press as: Chloé Rancoule, et al., Nanoparticles in radiation oncology: From bench-side to bedside, Cancer Letters (2016), doi: 10.1016/j.canlet.2016.03.011