Biochemical and Biophysical Research Communications xxx (2015) 1–5

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Review

Metals as radio-enhancers in oncology: The industry perspective

Agnès Pottier*, Elsa Borghi, Laurent Levy

Nanobiotix, 60 rue de Wattignies, 75012 Paris, France

ARTICLE INFO

Article history:
Received 4 September 2015
Accepted 5 September 2015
Available online xxx

Keywords:
Radio-enhancer
Nanotechnology
Cancer
Radiotherapy

ABSTRACT

Radio-enhancers, metal-based nanosized agents, could play a key role in oncology. They may unlock the potential of radiotherapy by enhancing the radiation dose deposit within tumors when the ionizing radiation source is 'on', while exhibiting chemically inert behavior in cellular and subcellular systems when the radiation beam is 'off'. Important decision points support the development of these new type of therapeutic agents originated from nanotechnology. Here, we discuss from an industry perspective, the interest of developing radio-enhancer agents to improve tumor control, the relevance of nanotechnology to achieve adequate therapeutic attributes, and present some considerations for their development in oncology.

Contents

1. Introduction

Oncology is a field of high unmet medical need. Cancer diseases are the second cause of death in the developed countries and are rapidly paralleled by developing countries [1]. The global cancer market was valued in 2010 at $54bn and forecasted to reach up to $81bn in 2016. The major drugs which contributed to the 2010 sales were the three blockbusters Roche's Avastin (bevacizumab) at $6.2bn, Herceptin (trastuzumab) at $5.2bn, and MabThera (rituximab) at $5.1bn [2]. Still, innovation is welcome for improved treatment in view of the multiple types of cancer. Huge investments are poured into research and development programs aiming at establishing effective therapies for long-term disease management and control. Nowadays, drug discovery should focus on treatments that offer not only the best risk-benefit ratio but also includes considerations such as the quality of cancer care, access to treatments, and differing stakeholders' expectations on therapies.

* Corresponding author.
E-mail address: agnes.pottier@nanobiotix.com (A. Pottier).

http://dx.doi.org/10.1016/j.bbrc.2015.09.027
0006-291X/

When possible, local treatment of cancer is sought. Surgery and radiation therapy are the mainstays of local treatment either used alone or in combination. About 60% of cancer patients receive radiotherapy at some point of their treatment regime. Despites of its widespread usage, radiation therapy presents a narrow therapeutic window. Most of the time, the total radiation dose required to eradicate tumor cells triggers unacceptable healthy tissues damage.

Recent developments involving radiotherapy equipment, softwares and the inclusion of image-guided radiation, have certainly improved the delivery of the radiation dose to the tumor [3–5]. Besides, an approach coming from within the cancer cells could unlock the potential of radiotherapy. As such, there are two possible ways to further improve local control with radiotherapy. The first approach relies on the use of radiation modifiers, such as radiosensitizers, which prepare the tumor cells to receive the radiotherapy, therefore increasing the tumor cell killing when radiotherapy is applied [6]. The second approach consists in the use of radio-enhancers which enhance the radiation dose deposit at the tumor cell level [7].

In this mini review we will discuss from an industry perspective, (1) the interest of developing a radio-enhancer, among other approaches, to improve tumor control, (2) show the relevance of nanotechnology to achieve adequate metal radio-enhancer attributes, and (3) present some considerations for development of metal-based nanoparticles as radio-enhancers in oncology.

2. Acting from within the cancer cells: radio-enhancers represent an attractive approach for successful tumor control

Radio-enhancer agents look promising in comparison with radiation modifier agents to locally improve tumor control. Coleman and Mitchell [8] raised critical considerations for successful combination of radiation modifiers and radiotherapy. To achieve the expected additive or synergistic effect of the combined treatment, one has to address a long list of questions such as, what is the radiation modifier target?, is the target stable?, can the target be reached?, what is the optimum schedule?, can the radiation modifier be used throughout a course of fractionated radiation therapy?, what is the selectivity of the agent?, what is the design of the clinical trial? and importantly how to keep the radiotherapy objectives in terms of local treatment since radiosensitizers, chemotherapeutic agents and biologicals, are so far systemic treatments impacting globally the health status.

In short, radiosensitizers are chemical or biochemical agents which rely on their specific interactions with cancer cells or tumor microenvironment. Therefore, any changes triggered by the radiotherapy itself may impact on the efficacy of the agent. Furthermore, a large set of preclinical research should be undertaken to implement a relevant schedule to optimize the combination treatment of radiotherapy with the radiosensitizer agent. This is an important phase of development because of the need of an appropriate design of clinical trials to establish the relevance of the combination. Also, the mode of action of most of radiation sensitizers is not specific to the tumor only.

In contrast, the design of radiation enhancer agents provides a different perspective. The purpose is no more to develop a compound with a chemical mode of action, on a specific target such as the cell cycle, DNA repair or pathways known in survival after radiation, in order to synergize with radiations. Instead, the aim is to design a compound which works through the same physical mode of action of radiotherapy, to enhance the radiation dose deposit. Ionizing radiations interact with tissues, mainly water molecules, and deposit energy via secondary electron emission (photoelectric and/or Compton effect), photon emission and also possibly via characteristic x-ray photon, Auger cascade and subsequent radical production. Introducing in the X-ray pathway a material with a high electron density will enhance the probability of interaction with ionizing radiation when compared to water, and will therefore achieve a higher energy dose deposit. Advancing in this concept, the previous list of questions intended for radiation modifier agents shifts into the following: can we design a radio-enhancer compound to be used throughout the course of fractionated radiation therapy to enhance the radiation dose deposit when the radiation beam is “on” and to be chemically inert in the cellular or subcellular systems when the radiation beam is “off”?

3. Metals as radio-enhancers: the values of nanotechnology

High Z metal elements (where Z is the atomic number and corresponds to the number of electron surrounding the nucleus) present the necessary features to interact strongly with ionizing radiation. Such key properties are not enough to manufacture an adequate radio-enhancer. Only the use of these high Z metal elements assembled as a high electron density material can make feasible the absorption/deposition of a high-energy dose when exposed to radiotherapy [9]. Beyond the selection of material composition and structure, well-controlled physico–chemical attributes of the object at the nanoscale, such as its size, shape and surface, can be independently optimized to determine its bioavailability and interactions with cells.

3.1. Nanoparticle size

The size is a fundamental parameter for nanoparticles transportation, accumulation and retention at the tumor site. Large inorganic nanoparticles (typically larger than 10 nm) tend to preferentially accumulate in the reticuloendothelial system, mainly liver and spleen. The particles' size limit for renal and lung barriers are reported around 5.5 nm and 34 nm respectively [10]. Passive tumor targeting generally relies on the enhanced permeability and retention (EPR) effect where the cutoff size of tumor transvascular pore is reported to be 100–200 nm [10,11]. The particle size is also key for efficient trafficking at the cellular and subcellular level. Metal-based nanoparticles with size around 50 nm have been reported to maximize cellular uptake [10]. Aggregation of nanoparticles in biological media has also been mentioned as participating to nanoparticles' cell uptake [12].

3.2. Nanoparticle shape

Remarkable nanoparticles accumulation within tumor vasculature has been shown using thin disc-like porous silicon particles with well-defined dimensions [13]. Regarding nanoparticles' cell uptake, spherical shape has been found more promising than rod shape for a high gold nanoparticles cancer cell uptake [14].

3.3. Nanoparticle surface

The surface of nanoparticles is a determinant parameter governing their interactions with biological systems. Stealth properties may be desired to prolong circulation using neutral hydrophilic polymers; on the contrary negatively or positively charged nanoparticles may be wanted for rapid and strong non-specific interactions with cells' membrane [15].

The optimal design of metal-based radiation enhancer agents should reconcile ambition and need: a radio-enhancer, at the right place, for the right time, at the right dose. Nanotechnologies may allow achieving such goals by separating different functions within a given object.

Please cite this article in press as: A. Pottier, et al., Metals as radio-enhancers in oncology: The industry perspective, Biochemical and Biophysical Research Communications (2015), http://dx.doi.org/10.1016/j.bbrc.2015.09.027

4. Metal-based nano-crystals as radio-enhancers: key requirements for development

Several guidelines have been proposed to ensure successful development of new tools to fight cancer. However, as part of the innovation phase and prior to moving into the development process, the following go/no go features are to be considered:

- Will this new tool bring solution to unmet medical need?
- How far does this new tool address all possible clinical settings?
- How far is this new tool integrated within the clinical practice?
- Can this new tool be manufactured in a reliable manner and in quantities to supply the potential market?

Each decision-parameter listed above break down into multiple bullet-points which converge into a unique "scope of work" as an entrance point to initiate the product development.

5. Considerations for development of metal-based nanoparticles as radio-enhancers in oncology

Unlocking the potential of radiotherapy would certainly bring new hope in cancer treatment. Several approaches have been explored to enlarge the therapeutic window of radiotherapy (Fig. 1). Among them, nanosized metal-based radiation enhancers, acting from within the cancer cell, emerge as an unprecedented alternative in therapy for local tumor control.

Selection of high Z elements constitute the fundamental for the design of nanosized radiation enhancers. From this point, selection of chemistry as opposed to screening the chemistry brings the added value to the compound.

5.1. A tool which may bring solution to unmet medical needs

"On" status: The high electron density of the material constituting the nanoparticle is a key feature, enabling a strong interaction with X-rays. Monte Carlo calculation is an effective tool to simulate the passage of ionizing radiations through matter and quantify radiation dose deposit in tissues. Simulations have shown the relevance of high Z materials to enhance radiation dose deposition with ionizing radiation sources classically used in the clinic [16]. Correspondingly, marked enhancement effects have been demonstrated in *in vitro* models supporting the development of these nanosized tools as effective radio-enhancers [17,18].

"Off" status: The integrity and inert behavior of the crystal are important parameters to consider in the development of nanosized radiation enhancers. Material with low solubility (no degradation), absence of redox phenomena or electron transfer (no oxidative damages) and no marked surface acido-basicity, will contribute to a safe design of the nanoparticle and ensure the quality and the outcome of the interaction with ionizing radiation upon multiple fractions of radiotherapy. In this regard, metal oxide nanoparticles offer a large panel of materials with tunable properties that may appear appealing when compared to stable high Z metal nanoparticles.

5.2. A tool which addresses a large panel of clinical settings

Metal-based radiation enhancers may be designed and developed to address all cancers. Here, a single design of nanoparticles for systemic administration may rely on the EPR effect to passively target all types of solid tumors.

Alternatively, metal-based radiation enhancers may be designed

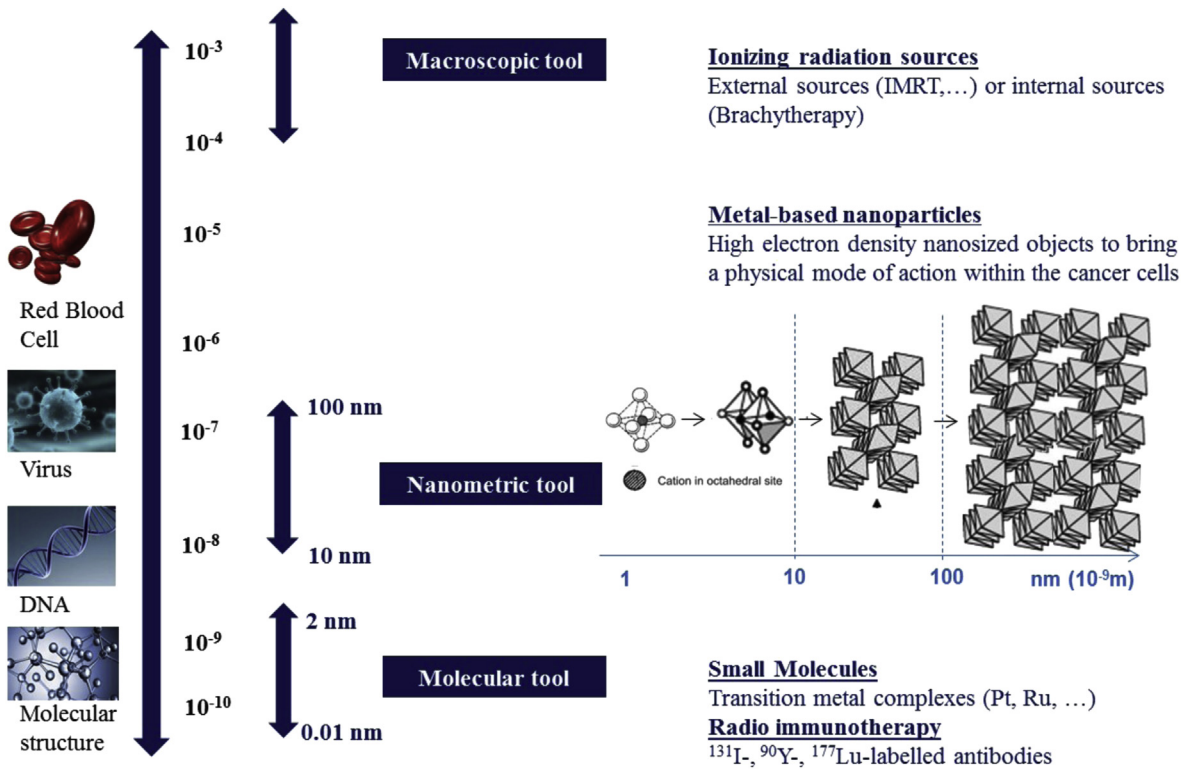

Fig. 1. Tools to enlarge the therapeutic window of radiotherapy. Macroscopic tools such as equipments, softwares, as well as the implementation of image-guided radiotherapy have improved the delivery of energy into the tumor. Still energy crosses healthy tissues. Molecular tools such as radiosensitizers are so far administered systemically to address local disease, impacting on global patient health. Nanometric tools may bring the same physical mode of action of radiotherapy at the cellular or subcellular level, therefore achieving the concept of local intervention to improve tumor control.

Please cite this article in press as: A. Pottier, et al., Metals as radio-enhancers in oncology: The industry perspective, Biochemical and Biophysical Research Communications (2015), http://dx.doi.org/10.1016/j.bbrc.2015.09.027

to meet specific clinical needs for different cancers. In this case, based on the same material core (composition and structure), therefore on the same physical mechanism of action, the nanoparticles may be functionalized and prepared for a given mode of application: local administration (intratumoral or superselective intra-arterial injection), intravenous, or direct application in the tumor bed during surgery after excising the tumor. In this context, the particular product will be selected on the basis of specific patient needs defined by the type of cancer, the stage of its course, and the optimum moment for therapy, i.e. preoperative, postoperative or definitive treatment (Fig. 2).

5.3. A tool which can be integrated in the clinical practice

Acceptance of a new treatment by the different oncology stakeholders is supported by its capacity to integrate the current clinical practice, which includes the patient's acceptance. Difficulties to adopt a new approach may typically come from the necessity to implement new or additional steps to existing practice.

When developing a metal-based nanosized radiation enhancer, one should typically consider the route of administration, frequency of use during the course of radiotherapy programs, and the timing between its administration and radiotherapy delivery. All these parameters may be sensitive for broad product adoption in the medical practice.

For instance, we have developed functionalized hafnium oxide nanoparticles intended for a single administration prior the onset of radiotherapy delivery and to persist in the targeted tumor during the complete radiotherapy program.

NBTXR3, our lead product has been designed for local use (intratumor or superselective intra-arterial injection). Proof of nanoparticles' dispersion, persistence within the tumor mass and absence of leak within the surrounding healthy tissues has been demonstrated in the non-clinical program [19]. These findings have been confirmed in the two ongoing clinical studies, in patients with soft tissue sarcoma and head and neck squamous cell cancer [20,21]. Here, 50 nm-sized hafnium oxide nanoparticles bear a negative surface charge, allowing for non-specific interactions with the cancer cells and a rapid binding and uptake by cells. Of importance, water for injection has been selected as media for the NBTXR3 nanoparticles to ensure both, an adequate dispersion of the nanoparticles in suspension (feasibility of the local administration) and, an adequate intratumoral dispersion.

5.4. A tool which can be manufactured in a reliable manner, to supply the market need

Selection of the manufacturing process is a key feature which should be considered at an early stage of development. Soft chemistry should be evaluated versus other manufacturing options which may require energetic processes. Each reaction steps should be in principle simple and easily tailored during the manufacturing process to ensure the reliability of the product specifications throughout all the production campaigns.

6. Clinical application

From an industry perspective, radio-enhancers as nanosized metal-based objects with well-defined composition and structure, could play a key role in oncology. They may unlock the potential of radiotherapy by two important features: their capacity to deposit high energy within tumors when the ionizing radiation source is ‘on’, and their chemically inert behavior in cellular and subcellular systems, demonstrated by very good tolerance, thus decreasing potential health hazards.

Important decision points support the development of these new type of therapeutic agents originated from the nanotechnology. Also, regulatory and stakeholders are actively working by bringing new guidelines and by participating to development programs for the benefit of patients [22–24].

Conflict of interest

All authors are employees of Nanobiotix and have financial involvement with Nanobiotix, which is developing the hafnium oxide nanoparticles presented in the manuscript. All authors are co-inventors of patent applications related to hafnium oxide nanoparticles presented in the manuscript.

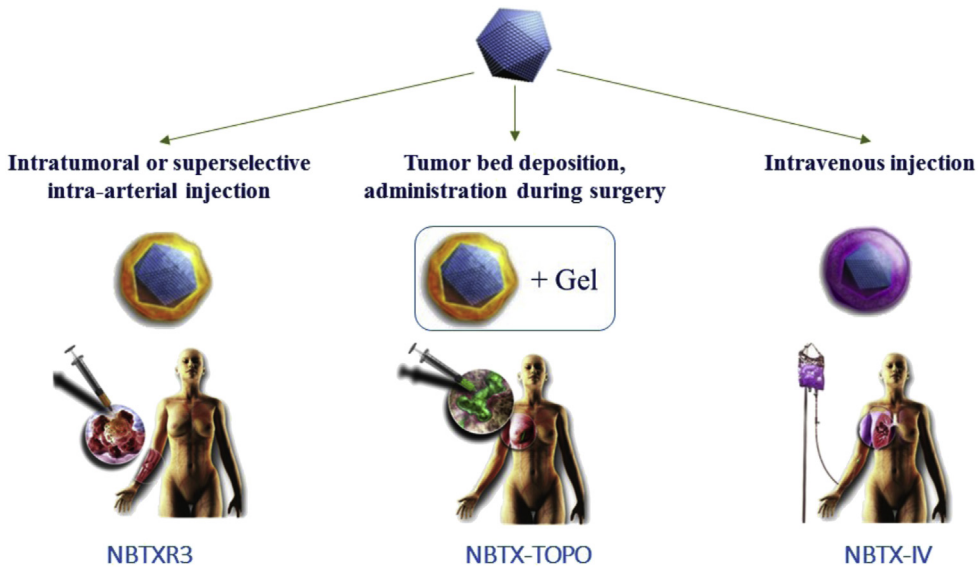

Fig. 2. Hafnium oxide nanoparticles as radio-enhancer. NBTXR3 is designed for local administration, intratumoral or superselective intra-arterial injection. NBTX-TOPO is designed for direct application in the tumor cavity. NBTX-IV is designed for systemic use, intravenous injection, opening the loco-regional approach.

Please cite this article in press as: A. Pottier, et al., Metals as radio-enhancers in oncology: The industry perspective, Biochemical and Biophysical Research Communications (2015), http://dx.doi.org/10.1016/j.bbrc.2015.09.027

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.09.027.

References

[1] Global Cancer Facts & Figures 3rd Edition, American Cancer Society Atlanta. A, 2015.
[2] The Cancer Market Outlook to 2016, Competitive Landscape, Market Size, Pipeline Analysis, and Growth Opportunities, Business Insights Ltd, 2011.
[3] D. Peiffert, A.S. Baumann, V. Marchesi, Treatment of hepatic metastases of colorectal cancer by robotic stereotactic radiation (Cyberknife®), J. Visc. Surg. 151 (2014) S45–S49.
[4] G. Sharp, K.D. Fritscher, V. Pekar, et al., Vision 20/20: perspectives on automated image segmentation for radiotherapy, Med. Phys. 41 (2014) 050902–050911, 50902-13.
[5] M. Brada, B. Haylock, Is Current Technology Improving Outcomes with Radiation Therapy for Gliomas? ASCO Educational Book, 2014, p. e89.
[6] D.E. Citrin, J.B. Mitchell, Altering the response to radiation: sensitizers and protectors, Semin. Oncol. 41 (2014) 848–859.
[7] A. Pottier, E. Borghi, L. Levy, New use of metals as nanosized radioenhancers, Anticancer Res. 34 (2014) 443–454.
[8] C.N. Coleman, J.B. Mitchell, Clinical radiosensitization: why it does and does not work, J. Clin. Oncol. 17 (1999) 1–3.
[9] M.K.K. Leung, J.C.L. Chow, B.D. Chithrani, et al., Irradiation of gold nanoparticles by x-rays: Monte Carlo simulation of dose enhancements and the spatial properties of the secondary electrons production, Med. Phys. 38 (2011) 624–630.
[10] J. Nam, N. Won, J. Bang, et al., Surface engineering of inorganic nanoparticles for imaging and therapy, Adv. Drug Deliv. Rev. 65 (2013) 622–648.
[11] H. Maeda, Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity, Adv. Drug Deliv. Rev. (2015 Jan 9), http://dx.doi.org/10.1016/j.addr.2015.01.002 pii: S0169-409X(15)00004-6.
[12] A. Albanese, C.D. Walkey, J.B. Olsen, et al., Secreted biomolecules alter the biological identity and cellular interactions of nanoparticles, ACS Nano 8 (2014) 5515–5526.
[13] A.L. van de Ven, P. Kim, O. Haley, et al., Rapid tumoritropic accumulation of systemically injected plateloid particles and their biodistribution, J. Control. Release 158 (2012) 148–155.
[14] B.D. Chithrani, A.A. Ghazani, W.C. Chan, Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells, Nano Lett. 6 (2006) 662–668.
[15] A.E. Nel, L. Mädler, D. Velegol, et al., Understanding biophysicochemical interactions at the nano-bio interface, Nat. Mater 8 (2009) 543–557.
[16] S.J. McMahon, W.B. Hyland, M.F. Muir, et al., Nanodosimetric effects of gold nanoparticles in megavoltage radiation therapy, Radiother. Oncol. 100 (2011) 412–416.
[17] R.I. Berbeco, H. Korideck, W. Ngwa, et al., DNA damage enhancement from gold nanoparticles for clinical MV photon beams, Radiat. Res. 178 (2012) 604–608.
[18] J. Marill, N.M. Anesary, P. Zhang, et al., Hafnium oxide nanoparticles: toward an in vitro predictive biological effect? Radiat. Oncol. 9 (2014) 150.
[19] L. Maggiorella, G. Barouch, C. Devaux, et al., Nanoscale radiotherapy with hafnium oxide nanoparticles, Future Oncol. 8 (2012) 1167–1181.
[20] S. Bonvalot, C. Le Pechoux, T. De Baere, et al., Phase I study of NBTXR3 nanoparticles, in patients with advanced soft tissue sarcoma (STS), J. Clin. Oncol. 32 (2014), 5s, suppl; abstr 10563.
[21] http://www.nanobiotix.com/news/release/nanobiotix-reports-positive-preliminary-results-in-head-and-neck-cancer-phase-iii-clinical-trial-with-nbtxr3/.
[22] M.A. Eaton, L. Levy, O.M. Fontaine, Delivering nanomedicines to patients: a practical guide, Nanomedicine 11 (2015) 983–992.
[23] F.J. Malinoski, The nanomedicines alliance: an industry perspective on nanomedicines, Nanomedicine 10 (2014) 1819–1820.
[24] R.M. Crist, J.H. Grossman, A.K. Patri, et al., Common pitfalls in nanotechnology: lessons learned from NCI's Nanotechnology Characterization Laboratory, Integr. Biol. 5 (2013) 66–73.

Please cite this article in press as: A. Pottier, et al., Metals as radio-enhancers in oncology: The industry perspective, Biochemical and Biophysical Research Communications (2015), http://dx.doi.org/10.1016/j.bbrc.2015.09.027