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NANOPARTICLES FOR DIAGNOSTIC IMAGING AND RADIOTHERAPY SPECIAL FEATURE: COMMENTARY

The future of nanosized radiation enhancers

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ABSTRACT

Radiotherapy has a universal and predictable mode of action, that is, a physical mode of action consisting of the deposit of a dose of energy in tissues. Tumour cell damage is proportional to the energy dose. However, the main limitation of radiotherapy is the lack of spatial control of the deposition of energy, that is, it penetrates the healthy tissues, damages them and renders unfeasible delivery of an efficient energy dose when tumours are close to important anatomical structures. True nanosized radiation enhancers may represent a disruptive approach to broaden the therapeutic window of radiation therapy. They offer the possibility of entering tumour cells and depositing high amounts of energy in the tumour only when exposed to ionizing radiations (on/off activity). They may unlock the potential of radiation therapy by rendering the introduction of a greater energy dose, exactly within the tumour structure without passing through surrounding tissues feasible. Several nanosized radiation enhancers have been studied in *in vitro* and *in vivo* models with positive results. One agent has received the authorization to conduct clinical trials for human use. Opportunities to improve outcomes for patients receiving radiotherapy, to create new standards of care and to offer solutions to new patient populations are looked over here.

WHAT IF WE COULD ENHANCE THE EFFECTIVENESS OF RADIOTHERAPY FROM WITHIN THE TUMOUR CELLS?

The question has been addressed for long time and still the efficacy of radiotherapy is limited by the tolerance of normal tissues adjacent to the tumour. In the past years, the development of radiotherapy equipment as well as dose calculation algorithms, the emergence of new delivery approaches, such as tumour tracking, have significantly improved the targeting of the delivery of the dose to the tumour only.[1] However, the energy always crosses healthy tissues, which ultimately limits the dose escalation. In parallel, novel approaches combining radiotherapy with modifier agents have been deployed.[2] Among them, radiosensitizers locally enhance the ability of radiations to kill tumour cells and work *via* a chemical mode of action on a specific tumour target to enhance the effectiveness of radiation. As such, they rely on the intrinsic biology of the tumour to ultimately kill the tumour cells. However, most of the time, they work without exposure to ionizing radiations, that is, they are active *per se*. Currently, they are administered by systemic routes, and thus, they have effects on other organs than tumour (off-target binding), which decrease the general patient's health status when the real need is the local radiosensitization. Therefore, the therapeutic window of the combined treatment, radiotherapy and radiosensitizer is hardly predictable and requires careful evaluation of normal tissue toxicity.

Recently, nanotechnology has created a new profile of interactions of materials with cell biology. Nanomaterials are able to interact and even to operate within cells. Nanosized objects with high electron density work *via* a physical mode of action, that of radiotherapy, and increase the probability of interactions with ionizing radiations as compared with water (on/off activity). Owing to their nanometric size, they are able to enhance the deposit of the radiation dose at the cancer cell levels. This innovative approach proposes to broaden the therapeutic window of radiation therapy.

Why do these nanosized agents represent a unique opportunity to determine the spatial (within the tumour structure) and time selectivity for radioenhancement (when the ionizing radiation beam is on)? Essentially, the chemical composition and structure of the nanoconstructs are key attributes controlling their interactions with ionizing radiation; more than the high atomic number (Z) of the chemical elements selected to construct the nano-objects, the overall high electron density of the material at the nanometric scale is crucial to achieve a high radiation dose deposit ("on" status). Monte Carlo simulation has shown enhancement effects of high-Z nanoparticles with energies traditionally used in radiotherapy practice.[3–5] While it is hardly possible to draw direct comparison between *in vitro* studies, the

observed enhancement values brought by these nanosized tools have suggested possibilities to improve the outcome of radiotherapy.[6–8] *In vivo*, intravenous injection of 1.9-nm-sized gold nanoparticles showed 86% survival at 1 year *vs* 20% for irradiation alone in EMT-6 mammary carcinoma mice model, using 250 kVp X-rays.[9] As well, intravenous injection of sub-5-nm-sized gadolinium-based nanoprobes (AGuIX®) showed median survival of 102.5 *vs* 44 days for irradiation alone in 9L tumour-bearing rats, using microbeam radiation therapy.[8] Owing to their small size, the accumulation of nanoparticles at the tumour site *via* the enhanced permeation and retention effect competed with their clearance, and irradiations were performed shortly (2 or 20 minutes) after injection to maintain a high concentration of nanoparticles in the tumour during treatment. 50-nm-sized hafnium oxide-based nanoparticles (NBTXR3) showed >70% survival at 120 days *vs* 0% for irradiation alone, in human colorectal carcinoma HCT-116 mice model using ^{192}Ir source. Also, significant overall survival was observed in human Ewing's sarcoma A673 mice model using ^{60}Co source. Single intratumour injections were performed followed by irradiation 24 h after. The size and negative surface charge of the nanoparticles were important attributes to ensure their intratumour bioavailability and persistence, with absence of leakage in surrounding healthy tissue during treatment.[3]

Specifically, the characteristics, size and shape, as well as surface properties, govern the interactions of these nanoconstructs with biological systems ("off" status). Thus, careful design of nanosized objects for true radiation enhancement embraces the control of their main properties, including the surface functionalization, which ultimately constitutes the interface for interactions with biological surfaces. Indeed, the optimal design of these anticancer agents should include nanoproducts that do not change during use (degradation) or generate new components, not only to achieve sustained intratumour availability during the whole radiotherapy delivery but also to ensure the concept of local intervention in oncology practice. Today, one nanosized radiation enhancer has received the authorization to conduct clinical trials for human use. A Phase I study has recently demonstrated that a single intratumoral injection of NBTXR3, followed by radiotherapy had a good safety profile in patients with locally advanced soft tissue sarcoma. Results demonstrated intratumour bioavailability of NBTXR3 over 5 weeks of radiotherapy with no leakage to the adjoining healthy tissues. The study has shown encouraging signs of antitumour activity in different sarcoma subtypes. The recommended volume for the Phase II/III trial was equivalent to 10% of the tumour volume.[10] In parallel, two Phase I studies in patients with locally advanced cancers of the oral cavity or oropharynx and in patients with unresectable rectal cancer are recruiting patients, and a Phase I/II clinical trial has been authorized in two new cancer populations—hepatocellular cancer and liver metastases.

In fact, the clinical development is just starting and nanosized radiation enhancers have yet to prove efficient translation from the laboratory to the clinic. The ongoing research and development will have a significant impact on the future of radiotherapy. If they realize their promises to improve the outcome for patients receiving radiotherapy (enhance efficacy), they may, in the longer term, open the access for efficient local treatment to patients whose tumour localization and constraints have excluded radiotherapy. They also may create new standards of care and offer solutions to new patient populations.

POTENTIAL TO IMPROVE THE OUTCOME FOR PATIENTS RECEIVING RADIOTHERAPY

Typically, in high-risk early-stage patients with prostate cancer, the current recommendation is androgen suppression therapy combined with radiotherapy because of potential for local recurrences and distant metastases. Increasing radiation dose to the prostate may improve local control and survival of these patients. However, rectum and bladder are also susceptible to receive a high-radiation dose, which would lead to a higher risk of complications. Thus, a radiotherapy technique using nanosized radiation enhancers could allow radiation dose escalation to the prostate while minimizing radiation to adjacent normal organs and therefore improve the therapeutic ratio.[11] However, nanoparticles' design as well as administration procedure should be carefully appraised to ensure their presence with adequate quantity at the tumour site and appropriate bioavailability prior to delivering the radiotherapy. Intralesional administration of nanoparticles when possible would fit with the concept of local intervention, providing their persistence within the tumour. On the other hand, systemic injections should guarantee the appropriate location of a high amount of nanoparticles at the tumour site prior to starting the radiotherapy. Moreover, the amount of time the nanoparticles has to be administered and the schedule between nanoparticle injection and the delivery of radiotherapy are important constraints which should be considered carefully for adoption of those nanosized radiation enhancers in current clinical practices. Evaluation of the benefit–risk ratio should be conducted based on a relevant non-clinical programme, which should include the evaluation of nanoparticles within the tumour *vs* healthy tissues or organs during treatment.

In the longer term, those nanosized radiation enhancers could allow for a reduction of the radiation dose to patients already receiving radiotherapy as per standard protocol. Hence, while keeping similar treatment efficacy, dose reduction could decrease the toxicity caused by ionizing radiations, in particular in the surrounding healthy tissues. It is well known that radiotherapy for early-stage breast cancer can reduce the rates of recurrence and of death from breast cancer. However, long-term follow-up in some trials[12] has shown that radiotherapy can also increase the risk of ischaemic heart disease, presumably through incidental irradiation of the heart. Therefore, clinicians may wish to consider cardiac dose and cardiac risk factors as well as tumour control when making decisions about the use of radiotherapy for breast cancer. Thus, a radiotherapy technique involving the use of nanosized radiation enhancers could allow for a radiation dose reduction to the heart while maintaining the radiation dose to the breast and therefore improve the therapeutic ratio.[12] To realize such ambition, proof of enhanced treatment efficacy should first be acknowledged. Evaluation of treatment benefit should be monitored using relevant biomarkers to ensure that patients will always

receive the best treatment. As for today, predictive biomarkers of later tumour response are to be found.

POTENTIAL TO CREATE NEW STANDARDS OF CARE

Nanosized radiation enhancers could bring new opportunities to those patients who developed cancers which cannot yet be treated with radiation therapy owing to the characteristics (typically the high radiosensitivity) of the tissues nearby the tumour. Radiotherapy has recently emerged has a promising treatment with a potential role across all stages of hepatocellular carcinoma (HCC), particularly for liver-confined HCC unsuitable for, or refractory to, other locoregional or systemic therapies. However, radiotherapy is generally not considered an option in HCC consensus documents or national guidelines, primarily because of the lack of Level 1 evidence. Besides, delivery of sufficient radiotherapy to control HCC while avoiding liver toxicity is a fine balance. Classic radiation-induced liver disease occurs between 2 weeks and 3 months after radiation therapy but may be avoided by a careful adjustment of the dose. However, patients with HCC with underlying liver disease (such as hepatitis and cirrhosis) usually develop non-classical radiation-induced liver disease, which is more difficult to prevent. In addition, non-hepatic normal structures (such as duodenum and bowel) also need to be considered because their tolerance appears lower in patients with HCC, and such organs may limit the dose of radiotherapy. Still, the potential is high for radiotherapy and radiation enhancers in a population whose damaged liver cannot adequately metabolize medicines and the physical mode of action may constitute a mainstay of treatment.[13]

POTENTIAL TO OFFER SOLUTIONS TO NEW PATIENT POPULATIONS

The possibility to use nanosized radiation enhancers could be of interest for elderly patients or for patients suffering from liver or kidney dysfunctions, which would prevent the use of other therapies such as chemotherapies or targeted therapies. Stereotactic body radiotherapy is recommended as an alternative to surgery for patients with early-stage non-small-cell lung cancer (NSCLC) who are medically unable to undergo or who refuse surgery. Also, definitive radiotherapy is an acceptable choice of treatment for patients aged $\geq$75 years with inoperable or unresectable NSCLCs. In these patient populations, nanosized radiation enhancers may provide a greater benefit without bringing additional toxicity of the treatment.[14]

In summary, nanosized radiation enhancers may render the introduction of a greater energy dose within the tumour structure feasible. A careful design of these nanotools, supported by an exhaustive non-clinical evaluation, is a key to ensure their successful translation from the laboratory to the clinic. Proof of enhanced efficacy has yet to be demonstrated in clinical trials to ensure the relevance of such concept. It is only then that the future of nanosized radiation enhancers with physical mode of action could be envisaged as a breakthrough approach for the benefit of patients.

CONFLICTS OF INTEREST

All authors are employees from Nanobiotix and have financial involvement with Nanobiotix, which is developing the NBTXR3 product presented in the manuscript. Agnes Pottier and Laurent Levy are co-inventors on a patent application related to the NBTXR3 material.

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