

Call to arms: need for radiobiology in molecular radionuclide therapy

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Dear Editor,

Now is an extraordinary time for the multidisciplinary field of molecular radionuclide therapy (MRT). Here, we make the case for increased efforts into researching the radiobiology of MRT.

More ~~cancer~~—patients than ever before are being treated with radiolabelled compounds than ever before and an increasing number of small and large pharmaceutical companies incorporate radiopharmaceuticals into their portfolios.

MRT allows specific irradiation of localised and disseminated disease with potentially fewer side effects than External Beam RadioTherapy (EBRT), albeit effects on organs involved in radiopharmaceutical excretion or showing natural uptake of the radiopharmaceutical cannot be discounted. The prime example of MRT is radio~~active~~ iodine, [¹³¹I]NaI, which is naturally taken up by the thyroid and used to treat various thyroid diseases, including cancer. [¹³¹I]NaI still encompasses up to 70% of all MRT treatments [1].

Another MRT success is achieved by relief of bone pain in metastasized cancer patients. ⁸⁹Sr, which initially replaced ³²P, has since itself been substituted with ¹⁵³Sm-lexidronam. ~~R~~However, recently, the alpha emitter ²²³Ra (²²³RaCl₂, Xofigo®, approved 2013) has become a clear winning strategy in treating bone metastases.

Most other MRT strategies utilise radio~~activity~~nuclides attached to tumour-targeting vectors or micro/nanoparticles. Examples include [¹³¹I]-mIBG (Azedra®, approved 2018) for neuroendocrine conditions and radiolabel~~l~~ed monoclonal antibodies, such

as [^{90}Y]Y-ibritumomab tiuxetan (Zevalin[®], approved 2002, now only used marginally) and [^{131}I]I-tositumomab (Bexxar[®], approved 2003, withdrawn 2014 due to limited use) for non-Hodgkin B-cell lymphoma, [^{177}Lu]Lu-DOTATATE (Lutathera[®], approved 2018) for neuroendocrine tumours and medical devices such as [^{90}Y]Y-labelled microspheres (SIR-Spheres[®], approved 2008, and TheraSphere[®], approved as Humanitarian Device 2012) for liver tumours. ~~[^{177}Lu]Lu-DOTATATE.~~ Other exciting breakthroughs in MRT include [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA for prostate cancer. Further radiopharmaceuticals are currently being studied in clinical trials and in discovery projects [2-3].

~~It is becoming increasingly~~ ~~Currently, it is clear~~ ~~that~~ some MRT patients are being over-treated (resulting in high levels of toxicity), ~~while some are~~ ~~or~~ under-treated (no tumour regression). The frequent ambiguity in predicting treatment outcome and inflexibility in altering set treatment regimens could lead to disease recurrence and avoidable treatment-related side effects that decrease quality of life and ~~increase~~ ~~later~~ illnesses (e.g. secondary cancers) ~~as well as and~~ avoidable costs under existing healthcare systems. For example, ^{223}Ra is now counter-indicated in combination with second-generation hormonal treatments, especially abiraterone. Aside from obvious improvements in radiochemistry, radiopharmacy, and dosimetry of MRT agents, a better understanding of the radiobiology, i.e. of the biological effects of ionising radiation used in MRT agents, ~~is~~ needed. Radiobiology of MRT is ~~needed~~ ~~necessary~~ to devise an optimised approach of use (~~with regards to~~ activity, therapy interval, vector, radionuclide etc.).

We postulate that, with better radiobiological understanding, MRT effectiveness could be enhanced and even progress from mostly palliative towards curative ~~use~~, for common as well as rare cancers, thus benefitting patients whilst simultaneously decreasing healthcare costs. Now is the time to exploit and expand upon the possibilities of the growing field of MRT, combine efforts between research groups, gain investment and create a research community around the radiobiology of MRT.

Six radiobiological objectives to understand MRT

Radiobiology has been key in establishing optimal treatment regimens for external beam radiotherapy (EBRT) whilst protecting healthy tissues. The paradigm of radiobiology is that tumour control probability and side effects are proportional to absorbed radiation dose; radiobiology is thus deeply connected with dosimetry. However, ~~breakthroughs~~ in EBRT effectiveness required radiobiology, which also considers dose fractionation, combination therapies, tumour radiosensitivity, ~~molecular biology~~, etc. [4]. Radiobiology has now progressed to further enhance EBRT effectiveness by considering novel combination therapies, including the use of radiosensitizers, such as genotoxic drugs or DNA damage repair inhibitors, hypoxia-altering therapies, immune checkpoint inhibitors, or radioprotectants.

These concepts ~~have not yet been investigated and~~ ~~are yet to be~~ applied to MRT.

Moreover, it is now obvious that extrapolation of radiobiology of EBRT to MRT is not straightforward, not only because of difference in dose-rate effects but also because

of activation of different molecular and cellular signalling pathways [5]. Arguably ~~though~~, radiobiology is evn more important for MRT than EBRT, considering radiopharmaceuticals are systemically administered ~~and encompass a group of treatments~~. Also, both additive and synergistic cytotoxic effects of vectors and radionuclides have to be considered. As an MRT radiobiological community, we therefore propose the following objectives to be explored for each therapeutic radiopharmaceutical:

Objective 1: Investigate the consequences of physical parameters on the therapeutic response. This includes the role of absorbed radiation dose assessment as a pre-requisite for establishing tumour control and normal tissue complication probability dose-effect curves, just as they exist ~~for EBRT in external beam exposure~~. Dose assessment is ~~also~~ a pre-requisite for ~~further~~ assessing the role of dose-rate, dose fractionation, and dose distribution [6], but also of non-dose-related phenomena such as the so-called non-targeted effects including bystander and systemic effects. For example, one contentious topic is the administration of [¹⁷⁷Lu]Lu-DOTATATE at fixed activities (7.4 GBq x 4), mimicking the treatment regimen used in the NETTER phase 3 trial, which arguably should be based ~~more~~ on more radiobiological research to ensure maximal therapeutic effectiveness.

This objective covers a hugely valuable field, which requires optimisation and standardisation, especially in light of the recent EU directive (European council directive 2013/59 Euratom [7]).

Objective 2: Determine the role of radiopharmaceutical and target distribution both at the subcellular and tissue level (tumour heterogeneity) using imaging as well as determining target expression, which is a prerequisite for radiotherapy efficacy and toxicity. Non-uniformity of the absorbed dose distribution results from uptake in physiologically functional sub-units and may lead to increased damage within these subcompartments leading to organ failure. Tissue and subcellular distribution of the radiopharmaceuticals also impacts the choice of the vector (e.g. internalising or not) but also of the subcellular target (e.g. nucleus, cell membrane, mitochondria etc.) and of the radionuclide (e.g. short or long particle range, high or low LET).

Objective 3: Determine the role of the tumour microenvironment and systemic reactions during MRT. Preliminary data indicate that, as for EBRT, bystander effects and systemic effects involving the immune system (both innate and acquired) have to be ~~considered and more deeply~~ investigated in more detail in MRT. Bystander effects include intercellular communication between targeted tumour cells (including cancer stem cells) and neighbouring cells including other tumour cells, cancer associated fibroblasts, and endothelial cells [8]. Those effects will lead to modifications in extracellular matrix structure and in perfusion with consequences on vector distribution and oxygen levels.

Objective 4: Identify biomarkers of therapy response. Every patient is unique and tumour characteristics will vary between patients, but also between different metastatic sites within one patient. Currently, every patient receives the same MRT

regimen based on cancer type. To optimize treatment outcome, biomarkers should be identified. These can be simple markers such as target level expression or proliferation, or can be more specific markers such as anomalies in cellular pathways changing radiosensitivity of the tumour or healthy tissues (e.g. DNA damage repair defects).

Objective 5: Determine optimal combination therapies, in particular, combinations of MRT with chemotherapy, immunotherapy, hormone therapy, or radiosensitizers. Combination of EBRT with a variety of these agents is common practice, and recently various (preclinical) studies have shown that MRT effects can be enhanced as well [9].

Objective 6: Determine effects of MRT on healthy tissues, both in the short and long-term. Radiopharmaceuticals accumulate not only in tumour cells, but also in healthy tissues via normal physiological excretion routes and/or receptor expression on healthy cells [10]. For example, radiolabelled PSMA-targeting agents accumulate not only in prostate cancer cells but also in salivary and lacrimal glands and the majority of radiopharmaceuticals are cleared from the body by the kidneys.

Our plan of action

Radiobiology of MRT is needed to optimise existing and new MRT strategies to their maximal clinical potential, efficacious in tumour cure whilst simultaneously safe for normal organs. ~~This includes acquiring the knowledge to design new radiopharmaceuticals to bind the right target, reach the right cell compartment, clear quickly without affecting efficacy whilst being able to tailor therapies to the individual patient. While this includes optimisation of target and vector choice, radiochemistry and dosimetry physics,~~ We now need to expand the field of radiobiology of MRT and form a large collaborative group to ensure clinical impact sooner rather than later. Now is the time to set up national initiatives and create a solid network that connects these at an international level. Hence, this call to arms.

So, calling all researchers in radiobiology and MRT, if you are interested in helping to establish a tight community with the aim to increase the input of radiobiology in existing and new MRT, we implore you to join our platform, which will foster radiobiology-oriented research in MRT by organizing symposia (first to be held in 2020), education and a potential network to apply for research grants. Partners for whom this would be interesting include radiobiologists, medical physicists, radiochemists, radiopharmacists, nuclear medicine clinicians, radiation oncologists, technologists, referring clinicians, radiation protection advisors, radioactive waste advisors, societies (EANM, ERRS), industry partners, and funding bodies where radiobiology is highlighted as a priority research area.

To conclude, ~~lets~~let us invest time, effort and money into this underexplored, but very essential, area of nuclear medicine research and put radiobiology of MRT on the map!

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