Nuclear medicine in cancer theranostics: beyond the target

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Oncologic nuclear medicine has come to fork in the road where a choice lies between being a peripheral diagnostic technique competing against ever-evolving anatomical imaging modalities in the detection of lesions or taking a central role in the revolution in precision medicine by characterizing tumour biology and directing treatment through use of highly specific tracers. The term theranostics encapsulates the integration of diagnostics and therapeutics in the individualized management of disease (*1*). Implicit in the theranostic paradigm is the assumption that results derived from a diagnostic test can precisely determine whether an individual patient is likely to benefit from a specific treatment. This underpins recent focus on companion diagnostics as an integral part of drug development. The requirement for demonstration of the presence of human epidermal growth factor receptor 2 (HER2) on a tumor in the selection of candidates for trastuzumab therapy (Herceptin®) is an excellent example of the concept of theranostics in oncology but is limited by the potential for sampling bias intrinsic in tissue biopsy. Molecular imaging of HER2 expression using radiolabeled trastuzumab provides an alternative vision of how the selection of expensive and sometimes toxic therapies might look in the future (*2*). Due to its whole body imaging capability, molecular imaging with ^{89}Zr-trastuzumab can be used to detect heterogeneity of HER2 expression and therefore has the potential to better select patients for Herceptin® and antibody-drug conjugate therapy using this target (*3*) but also opens the way for therapeutic application of radionuclide therapy (*4*). Beyond the expected clinical benefits of personalized medicine, theranostics could also have a significant positive economic effect. For example, KRAS is an oncoprotein that acts downstream of the epidermal growth factor receptor, and thereby predicts a poor response to anti-EGFR (epidermal growth factor receptor) therapies. The implementation of KRAS mutation status as a companion test to exclude patients unlikely to benefit from such therapies has been estimated save a net cost of $7,500 to $12,400 per patient in the United States and €3,900 to €9,600 per patient in Germany, with equivalent clinical outcomes (*5*). This economic impact becomes particularly relevant if one were contemplating introducing relatively expensive imaging biomarker studies. Given the huge relative costs of modern cancer therapies, the costs of imaging could be more than adequately offset by preventing futile or unnecessary treatments.

Nuclear medicine is ideally placed to play a central role in theranostics by allowing visualization of molecular targets and thus performing so-called *in vivo* immunohistochemistry and thereby providing non-invasive biomarkers to select and monitor responses to targeted drugs,

particularly agents labeled with therapeutic radionuclides. The staging and treatment of thyroid cancer with the diagnostic use of ^{123}I or ^{124}I complementing the therapeutic efficacy of ^{131}I has paved the way for theranostics in therapeutic nuclear medicine. Successful treatment of metastatic thyroid cancer was achieved even before the molecular basis of radioiodine uptake through the sodium-iodide symporter was characterized, speaking to the power of this paradigm. The use of radiolabeled MIBG in diagnosis and treatment of metastatic neuroblastoma, paraganglioma and phaeochromocytoma or of radiolabelled somatostatin analogues in neuroendocrine tumors (NETs) has extended the paradigm to other cancers. Despite the impressive results achieved using these agents, they have generally been developed in academic centers and used on a compassionate basis. This has led to limited resources for establishing the evidence base that usually accompanies registration and approval of cancer therapies. In particular, there has been a lack of randomized control trial (RCT) data comparing radionuclide therapies with other forms of therapy and virtually none testing the integrated theranostic approach. This failing in the eyes of the oncology community has recently been addressed in small intestinal NET, following recent presentation of the results of the NETTER-1 study at the 2016 Gastrointestinal Cancer Symposium of ASCO GI. Briefly, the NETTER-1 study is a RCT that compared ^{177}Lu-DOTATATE (4 administrations of 7.4 GBq) with an augmented dose of octreotide long-acting release (60 mg) in patients with progressive, somatostatin-receptor-expressing mid-gut NETs (ileal in 75% of cases). The interim analysis is very encouraging for ^{177}Lu-DOTATATE, with an objective response of 19 % (vs 3%), increased progression-free survival (not reached but estimated to be 40 for Peptide Receptor Radionuclide Therapy-PRRT vs 8.4 months with augmented-dose octreotide long-acting release). Although there is as yet no RCT evidence support the utility of an increased dose of somatostatin analogues as an anti-proliferative therapy, it is interesting to note that the majority of previously progressing patients in this arm of the trial achieved disease stabilization on this therapy, supplementing data from the PROMID (6) and CLARINET (7) studies that suggest that these agents can themselves delay disease progression. This makes the results even more impressive than those achieved using targeted agents, which have generally been tested against placebo. Although the overall survival data are not yet mature and median survival has not been reached in either arm, there was reduced mortality in the PRRT arm (13 vs 22 cases). Importantly for an essentially palliative therapy, the toxicity profile of PRRT was acceptable. We believe that these data will provide a

powerful impetus for wider application of the ^{68}Ga/^{177}Lu-DOTATATE strategy in the management of inoperable grade 1-2 intestinal NETs that progress despite use of somatostatin analogues. Clinical trials comparing ^{177}Lu-DOTATATE to small molecule inhibitors in pancreatic NETs are currently ongoing. Likewise, somatostatin receptor antagonists have also provided very promising results for somatostatin receptor targeting (*8*) but these will likely require head-to-head comparison with other treatments of NET to assess their relative efficacy and toxicity. These encouraging results have expanded the scope of theranostics to other targets such as ^{68}Ga/ ^{177}Lu-labeled PSMA (prostate specific membrane antigen) ligands in prostate cancer (*9*) or ^{68}Ga/^{177}Lu-labeled CXCR4 ligands in myeloproliferative syndromes and solid tumors (*10*).

If we are to establish the theranostic paradigm as a valid method of treating cancers we believe that it is important to learn from both the successes and failures of the past. The evolution of thyroid cancer management provides an illustrative example of the key principles that are required to advance a theranostic approach. These include:

1- Optimal patient selection. This must be based not only on a knowledge of target expression but also of other prognostic factors that influence outcomes, which might include the presence and biological behavior of subclones of cells lacking target expression, tumour burden and location. For radioiodine therapy these factors include the presence of non-iodine-avid lesions, particularly those with intense ^{18}F-FDG uptake, a short doubling time of thyroglobulin, large tumor volumes, the presence of bone metastases, and significant local invasion. For PRRT, spatial discordance in SSTR and FDG-avidity of lesions, disease burden and proliferative activity, and possibly site of primary origin are corresponding factors that need to be considered.

2- Although not yet widely applied or clearly validated, optimization of the therapeutic index by prospective dosimetry is a desirable objective. Wider availability of ^{124}I potentially enables this for ^{131}I therapy and quantitative single-photon emission computed tomography/computed tomography (SPECT/CT) or longer lived SSTR-ligands such as ^{64}Cu-labeled SST analogues might make this feasible for PRRT.

3- The ability to pharmacologically manipulate target expression. For radioiodine therapy this involves up-regulation of iodine transporter expression by increased TSH (thyrotropin) levels (endogenous or exogenous) and more recently through use of tyrosine

kinase inhibitors in the MAPK kinase pathway in iodine-refractory throid cancer (*11*). For PRRT, somatostatin analogue therapy may influence SSTR-expression.

4- Use of cytostatic treatments between and following radionuclide therapy. For example, use of supra-physiologic thyroid hormone replacement to achieve thyrotropin suppression following radioactive iodine. For PRRT, ongoing use of somatostatin analogues may delay recrudescent disease based on data from the PROMID and CLARINET studies cited above.

5- Optimal follow-up of patients by the use of accurate and reliable markers of therapeutic efficacy. For ^{131}I this includes decreasing serum thyroglobulin and decreased and preferebaly absent radioiodine uptake sites in post-therapy scintigraphy with concomitant absence of morphologic progression or resolution of targeted lesions. Similarly for PRRT, chromogranin A and any specific bioamine or hormone produced by functioning NET combined with repeat somatostatin receptor imaging provide evidence of response in combination with anatomical imaging.

Therefore, despite being somewhat specific, the radioiodine theranostic model should serve as the template for improving the efficacy of and evidence–base for therapeutic nuclear medicine. Although immediately applicable to PRRT, it is also relevant for a range of other radionuclide therapies. There is particular excitement, for example, for targeting prostate specific membrane antigen in prostate cancer but we need to ensure that this is developed in a rigorous, scientific environment that defines the optimal therapeutic windows, optimizes tumor targeting and radiopharmaceutical delivery, minimizes radiation exposure to at-risk organs (e.g., dosimetry-based, mathematical modelling), selects the most suitable isotopes according to the tissue compartment to be targeted (Auger electrons, alpha and beta emitters), identifies agents that can modulate target expression or increase radiation-induced cellular damages (radiosensitizing agents), and encourages the combination of cytostatic treatments between radioactive sessions while identifying reliable and accurate biomarkers of therapeutic response. In order to achieve all of this, an active collaboration between different implied disciplines is necessary.

Compliance with ethical standards

NA

Conflicts of interest

The authors have nothing to disclose.

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