Radionuclide Theranostics in Cancer

AUTHOR(S)

Delphine Denoyer, N Pouliot

Radionuclide Theranostics in Cancer

Delphine Denoyer[1]* and Normand Pouliot[2,3,4]

[1]Metals in Medicine Laboratory, Centre for Cellular and Molecular Biology (CCMB), Melbourne Burwood Campus, Deakin University, VIC, Australia
[2]Metastasis Research Laboratory, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[3]Pathology Department, University of Melbourne, VIC, Australia
[4]Sir Peter MacCallum Department of Oncology, University of Melbourne, VIC, Australia

Knowledge of the molecular profile of a tumor not only guides clinical decisions for optimal treatment but can be harnessed also to monitor treatment response objectively. In this respect, theranostic approaches for the diagnosis and treatment of a variety of tumor types are rapidly gaining momentum. By combining diagnostic imaging modalities with therapeutic interventions directed against the same molecular target, theranostics enables selection of patients more likely to respond to a specific therapy and consequently improves the therapeutic/toxicity ratio while avoiding unnecessary treatment [1].

Molecular imaging using radioisotopes is now commonly used for non-invasive detection of specific tumor targets. By replacing the imaging isotope (i.e., gamma or positron emitters) with alpha, beta or auger-electron emitters, a specific probe is turned into a powerful therapeutic agent. Interestingly, using diagnostic/therapeutic pairs is not a new concept in the nuclear medicine field. For more than 60 years, $^{123}I/^{131}I$ has been employed for the diagnosis and radionuclide therapy of well-differentiated thyroid cancers. More recently this principle has been applied to neuroendocrine tumors using compounds specifically targeting somatostatin receptors (SSRT)for both imaging and peptide receptor radionuclide therapy (PRRT) [2]. The nuclear medicine community has enthusiastically embraced the use of the pair $_{68}$Ga-DOTATATE (PET imaging)/^{177}Lu-DOTA-octreotate (PRRT) which proved successful in multiple nuclear medicine centres [2,3]. Can theranostic strategies be extended to other tumor types? Current evidence in preclinical models of breast cancer and melanoma and from clinical studies suggests that theranostic targeting of these solid tumors and/or associated angiogenic switch could benefit patients.

Several preclinical proof-of-concept studies have now validated extracellular melanin as a suitable target for imaging and radioimmunotherapy (RIT) [4]. In a recent phase Ia/Ib clinical trial, the melanin-binding ^{188}Re-6D2 monoclonal antibody was well tolerated, showed only mild haematological toxicity and improved patient survival [5]. Cell permeable benzamide derivatives such as ^{18}F-MEL050 may further improve imaging of pigmented melanoma since they recognize both intra- and extracellular melanin. Early preclinical work evaluating benzamide derivatives diagnostic/therapeutic pairs in mouse melanoma models is promising [6,7] but further clinical trials are required to assess whether these could improve clinical outcome in patients with pigmented melanoma.

Integrin receptors, most notably αvβ3, appear particularly well suited for selection of patients and early validation of treatment response to anti-angiogenic therapy. The monomeric compound, ^{18}F-Galacto-RGD was the first integrin-specific PET tracer to be evaluated as a non-invasive probe for imaging of tumor angiogenesis in a clinical trial and showed good tumor uptake and favourable pharmacokinetics characteristics [8]. Second generation multimeric integrin-binding compounds with improved biodistribution and higher tumor uptake are now being investigated for imaging and radionuclide therapy. Treatment of tumor-bearing mice with these compounds labeled either with ^{111}In or ^{90}Y results in significant growth delay [9]. However, high accumulation of multimeric RGD peptides, in organs such as the spleen, liver and kidneys limits the dose that can be administered. Liu and co-workers recently showed that this problem can be partially overcome by insertion of Gly_3 and PEG_4 linkers into RGD dimers. These RGD dimeric complexes demonstrated similar affinity for αvβ3 integrin to tetrameric RGD but lower retention in non-target organs and as a result, were less toxic [10,11].

The introduction of nanocarriers (i.e., dendrimers, nanoparticles, liposomes) targeted via RGD peptides has expanded the range and specificity of theranostic currently available and significantly improved the therapeutic efficacy of anticancer drugs. Accumulation in the reticuloendothelial system of the liver, spleen or lymph nodes remains a limitation of this method that needs to be overcome. This can be reduced in part by PEGylation of nanoparticles. Inducible nanoparticles represent another exciting development in this field [12].

Toxicity to normal organs observed with radionuclide therapy highlights the importance of accurate dosimetry. Here again, major advances have been made with the introduction of PET radionuclides with long half-lives such as ^{64}Cu (12.7 hours) that, unlike radionuclides with short half-life (i.e., $_{68}$Ga, 68 minutes), allows long term dosimetry. For individualized patient dosimetry, the same element should be used for imaging and therapy to better reflect the biodistribution of the therapeutic radiotracer. Development of simplified chemistry for the synthesis of more stable ^{64}Cu/^{67}Cu-labeled imaging and therapeutic radiotracers will most likely facilitate their translation to the clinic [13].

The genetic and phenotypic heterogeneity of tumours and the activation of alternative signalling pathways in response to targeted therapies all contribute to the development of drug resistance and treatment failure. Will radionuclide-based theranostics targeting a single biomarker suffer the same faith? While in theory this approach is powerful, clinical evidence indicates that drug resistance to targeted therapy almost inevitably occurs (e.g. BRAF inhibitors for the treatment of melanoma or Tamoxifen for the treatment of ER-positive breast cancer). Current clinical trends to overcome the issue of resistance are to combine inhibitors blocking multiple signalling pathways. It will be interesting to see if "combination theranostics" utilising radionuclides directed towards multiple molecular targets will be sufficient to prevent the emergence of resistance. If so, the next challenge will be to identify the best combination therapies and optimisation of treatment regimens.

*Corresponding author: Dr. Delphine Denoyer, Deakin University, Melbourne Burwood Campus, 221 Burwood Highway, Burwood, VIC 3125, Australia, Tel: 61 3 9244 6027; E-mail: d.denoyer@deakin.edu.au

In conclusion, medical and technological advances are rapidly changing our approach to cancer diagnosis and treatment. While theranostics is still at an early stage of implementation, there is little doubt that over the next decades its use will become increasingly part of the standard of care for cancer patients as we move towards personalized therapy. Other challenges ahead are likely to be economic rather than scientific, due to regulatory issues and the cost of such procedures.

References

1. Kelkar SS, Reineke TM (2011) Theranostics: combining imaging and therapy. Bioconjug Chem 22: 1879-1903.

2. Baum RP, Kulkarni HR (2012) THERANOSTICS: From Molecular Imaging Using Ga-68 Labeled Tracers and PET/CT to Personalized Radionuclide Therapy - The Bad Berka Experience. Theranostics 2: 437-447.

3. Hicks RJ (2010) Use of molecular targeted agents for the diagnosis, staging and therapy of neuroendocrine malignancy. Cancer Imaging 10 Spec no A: S83-S91.

4. Jandl T, Revskaya E, Jiang Z, Bryan RA, Casadevall A, et al. (2013) Complement-dependent cytotoxicity of an antibody to melanin in radioimmunotherapy of metastatic melanoma. Immunotherapy 5: 357-364.

5. Klein M, Lotem M, Peretz T, Zwas ST, Mizrachi S, et al. (2013) Safety and efficacy of 188-rhenium-labeled antibody to melanin in patients with metastatic melanoma. J Skin Cancer 2013: 828329.

6. Denoyer D, Greguric I, Roselt P, Neels OC, Aide N, et al. (2010) High-contrast PET of melanoma using (18)F-MEL050, a selective probe for melanin with predominantly renal clearance. J Nucl Med 51: 441-447.

7. Denoyer D, Lobachevsky P, Greguric I, Hicks RJ (2013) Targeting melanin for imaging and treatment of melanoma metastases. 18th World Congress on Advances in Oncology and 16th International Symposium on Molecular Medicine (Poster #208)

8. Beer AJ, Haubner R, Sarbia M, Goebel M, Luderschmidt S, et al. (2006) Positron emission tomography using [18F]Galacto-RGD identifies the level of integrin alpha(v)beta3 expression in man. Clin Cancer Res 12: 3942-3949.

9. Janssen ML, Oyen WJ, Dijkgraaf I, Massuger LF, Frielink C, et al. (2002) Tumor targeting with radiolabeled alpha(v)beta(3) integrin binding peptides in a nude mouse model. Cancer Res 62: 6146-6151.

10. Liu Z, Shi J, Jia B, Yu Z, Liu Y, et al. (2011) Two ^{90}Y-labeled multimeric RGD peptides RGD4 and 3PRGD2 for integrin targeted radionuclide therapy. Mol Pharm 8: 591-599.

11. Liu Z, Wang F (2013) Development of RGD-Based Radiotracers for Tumor Imaging and Therapy: Translating from Bench to Bedside. Curr Mol Med 13: 1487-1505.

12. Lee DY, Li KC (2011) Molecular theranostics: a primer for the imaging professional. AJR Am J Roentgenol 197: 318-324.

13. Paterson BM, Roselt P, Denoyer D, Cullinane C, Binns D, et al. (2014) PET imaging of tumours with a 64Cu labeled macrobicyclic cage amine ligand tethered to Tyr3-octreotate. Dalton Trans 43: 1386-1396.