The Promise of Lu-177-based Radiotherapies

Rodney J. Hicks, MB, BS (Hons), MD, FRACP, FAHMS; Michael S. Hofman, MBBS, FRACP, FAANMS; Amir Irvani, MD, FRACP; Grace Kong, MD — Peter MacCallum Cancer Centre, Melbourne, Australia

Although the early history of radionuclide therapy was dominated by iodine-131, more recently lutetium-177 has become the poster-child of therapeutic nuclear medicine. \[^{177}\text{Lu-DOTA}^\text{Tyr^3}\] Octreotate (\[^{177}\text{Lu-DOTATATE}\] peptide receptor radionuclide therapy (PRRT) led the way\(^1\). Multiple studies have demonstrated PRRT to be an effective treatment for advanced neuroendocrine neoplasms (NEN) with high somatostatin receptor (SSTR) expression\(^2\). Substantial tumor regression can be observed even in patients with advanced disease (Figure 1). PRRT is generally well-tolerated with Myelodysplastic syndrome (MDS)/leukaemia being the most serious but uncommon (<2%) potential long-term risk\(^3,4\). A recent prospective randomised-control trial (NETTER-1) has confirmed the superiority of \[^{177}\text{Lu-DOTATATE}\] compared to high-dose somatostatin analogue therapy in inoperable Grade 1-2 midgut NET\(^5\). Other SSTR-expressing tumors are also potentially amenable to PRRT, including pheochromocytoma/paraganglioma (PCC/PGL)\(^6-9\), with a prospective trial in progress (ClinicalTrials.gov identifier NCT03206060). Limited retrospective series have also shown encouraging symptomatic responses and disease control in pediatric patients with relapsed or refractory neuroblastoma\(^10,11\). Again, a prospective trial is in progress to further establish its role in this complex disease. More recently, there has been evidence that radiolabelled SSTR2 antagonists generate higher tumor doses and more DNA double-strand breaks than agonists, resulting in better treatment efficacy despite poor internalisation\(^12,13\). \[^{177}\text{Lu-DOTA}^\text{JR11}\] (\[^{177}\text{Lu-OPS201}\]) is currently being evaluated in an phase 1-2 multicentre study (ClinicalTrials.gov identifier NCT02592707)\(^14\). Despite its promise and having been administered to thousands of patients globally, PRRT has taken over two decades to get to a point where reimbursement appears likely in some jurisdictions. This is largely because most trials have been
Lu-177-based Radiotherapies (Continued from page 1).

with multiple myeloma 19-21 as well as some solid tumors including lymphoma, leukemia and up to two-thirds of patients with small cell carcinoma of the lung and adrenocortical carcinoma 22-23. 177Lu-pentixather has been developed recently and used in two small retrospective, single-institutional reports with differing treatment protocols, unclear eligibility criteria, and inconsistent follow-up and outcome measures.

If other 177Lu radionuclide therapies are to enter more rapidly into routine clinical practice, we, as a nuclear medicine community, must do better in providing our oncology colleagues and funding authorities with high-quality, prospective randomised data. For prostate cancer, vast opportunity exists because the overwhelming majority of castrate-resistant metastatic disease expresses high levels of prostate specific membrane antigen (PSMA), which can be targeted therapeutically with small molecule ligands labelled with 177Lu15. Impressive results are seen in individual patients (Figure 2). Randomised trials are now required comparing this therapy to existing standards of care. A phase II, 200 patient, multi-centre randomised Australian trial comparing Lu-PSMA to cabazitaxel will commence shortly, and other international trials are planned.

If one overcomes the financial and regulatory hurdles involved, the therapeutic potential of 177Lu-labeled agents is only limited by the imagination. As our understanding of cellular targets increases, so too do the potential theranostic options. Of the evolving targets under investigation, CXCR4 and bisphosphonates are of interest. The former is a G protein-coupled protein receptor C-X-C chemokine receptor 4 (CXCR4) and overexpressed in many solid and hematologic cancers. Binding to its ligand (CXCL12) activates a downstream signaling pathway, which is critical in cell proliferation, angiogenesis, development of metastasis, and survival16-18. CXCR4 is expressed in various hematological neoplasms including lymphoma, leukemia and up to two-thirds of patients with multiple myeloma19-21 as well as some solid tumors including small cell carcinoma of the lung and adrenocortical carcinoma22-23. 177Lu-pentixather has been developed recently and used in two small pilot studies in patients with highly refractory multiple myeloma with encouraging results24-26. CXCR4-targeted theranostics in advanced lymphoproliferative cancers is currently under way in a multicenter prospective phase 1/II study in Europe (COPRIT trial, Eudra-CT 2015-001817-28). Bisphosphonates can be used to deliver the radionuclides to bone tissue because of their exceptional affinity for hydroxyapatite. 177Lu-Labeled sodium pyrophosphate (177Lu-PYP), has been synthesized for use in treatment of bone pain related to skeletal metastases27. These agents have been used in animal models, and human studies are awaiting.

While spatial and temporal heterogeneity of expression of targets in cancer cells remains one of the main challenges of targeted therapy, some cancers express multiple receptors concomitantly. For instance, recent in vitro studies have shown that, in addition to SSTR, other peptide receptors are overexpressed in NET28. For example, the incretin receptor, glucagonlike peptide 1 (GLP-1) receptor and glucagon receptor are overexpressed in insulinomas, and glucose-dependent insulinotropic polypeptide (GIP) receptor and CCK2 receptors are overexpressed in gastroenteropancreatic (GEP) NETs29-31. A recent autoradiography study measuring GLP-1, GIP, and SSTR receptors concomitantly in the same GEP NET sections showed that all three types of receptors were often co-expressed. This would have allowed acquisition of a highly homogeneous tumor targeting while a single radioligand would show only a heterogeneous patchy uptake27. Homogenous delivery of the Lu-labelled peptide could thus potentially overcome tumor heterogeneity. Multi-receptor targeting could potentially be achieved by bi/heteromultivalent ligands, cocktail of ligands or sequential radioligand administration30.

Finally, optimization of tracer delivery may be achieved by direct targeting of the metastatic site by different routes of administration, for instance by hepatic intra-arterial, intraperitoneal or intrathecal injections.

The complete list of references is posted on the CTN website.
Message from the Co-Chairs:
The Growth of Theranostics

Theranostics, the use of diagnostic procedures to select and guide targeted therapies, has a long tradition in nuclear medicine. Radiiodine is a prototypic example of the theranostic approach with both diagnostic and therapeutic applications in hyperthyroidism and differentiated thyroid cancer. The recent development of radionuclide therapies targeting somatostatin receptors in neuroendocrine tumors (NETs) and prostate-specific membrane antigen (PSMA) promises to make new, high-impact classes of theranostic agents clinically available. In both cases, diagnostic imaging to confirm the presence of the molecular target is a prerequisite for subsequent radionuclide therapy. Examples of somatostatin receptor imaging with $^{68}$Ga-DOTATATE and PSMA imaging with $^{68}$Ga-PSMA-11 are shown in Figures 1 and 2. By changing the radiometal to Lu-177 or another therapeutic radionuclide, these imaging agents can be converted to therapeutic agents. While anatomic imaging can demonstrate the presence of viable tumor, specific molecular imaging agents are needed to demonstrate the presence of the therapeutic target.

Since 2012, the Clinical Trials Network (CTN) has organized the Gallium-68 Users Group meeting that connects individuals from academia, industry, and the FDA to discuss progress, challenges and upcoming initiatives in the field. Additionally, the CTN continues to be actively involved in supporting the availability of $^{68}$Ga-labeled radiopharmaceuticals, the clinical trials needed to support regulatory approval and reimbursement, and the education of nuclear medicine professionals to use these agents in clinical practice. More recently, the CTN has worked with collaborators in academia to develop a clinical protocol to harmonize trials performed with $^{68}$Ga-PSMA-11 and other small molecule PSMA ligands. As radionuclide therapies targeting somatostatin receptors and PSMA reach advanced stages development, the CTN is partnering with academic institutions and commercial entities to advance these theranostic agents.

While there is much excitement in the nuclear medicine community regarding theranostics, high-quality clinical trial data are needed to gain acceptance of these therapies by other clinicians. The NETTER-1 trial showing the therapeutic efficacy of Lu-177 DOTATATE for treating somatostatin receptor-positive midgut neuroendocrine tumors is a good example of the type of study needed to advance theranostics in routine clinical use. The nuclear medicine community will need to work effectively with surgeons, radiation oncologists and medical oncologists to integrate theranostics into existing and emerging treatment algorithms. The SNMMI and CTN are well-positioned to continue providing education and expertise to other medical professionals regarding the value and the utility of theranostics in clinical practice.

Reference:
Peptide receptor radionuclide therapy (PRRT) is now very well established as an effective form of treatment for patients with non-operable neuroendocrine tumors (NETs). This therapy has led to modest objective response rates and, perhaps more importantly, notable symptomatic and survival advantages. PRRT with either 90Y-DOTA Phe1-Tyr3-octreotide (90Y-DOTATOC) or the alternative 177Lu-DOTA Phe1-Tyr3-octreotate (177Lu-DOTATATE) is endorsed by both the European and the North American neuroendocrine tumor societies for the treatment of patients with progressive refractory disease.

Either the DOTATATE or DOTATOC targeting peptide can be labeled with 90Y, and it is unlikely that there is any clinically meaningful differences in the effectiveness between the two. Both peptides avidly target the type 2 somatostatin receptor highly expressed on the surface of neuroendocrine tumor cells. 90Y-DOTATOC has demonstrated substantial efficacy and limited toxicity in patients with metastatic NETS. Traditionally, 90Y-DOTATOC is delivered in multiple 120 mCi treatment cycles separated by 10 to 12 weeks to allow for bone marrow recovery and to limit renal damage. Infusion of this therapeutic agent is performed while the patient receives an intravenous solution of cationic amino acids to reduce uptake by the kidneys. Amino acid solutions consisting of only arginine and lysine are very well tolerated by patients. Because this radionuclide does not emit gamma rays, radiation safety guidelines allow patients to be treated and released on the same day.

90Y has a 64-hour half-life and a high-energy beta particle with an Ebeta max of 2.3 MeV. There is good evidence that 90Y is more effective than 177Lu for treatment of larger tumors, yet less effective for smaller tumors that should respond better to targeting with 177Lu. The reason for this relates to the longer path length associated with the highly energetic beta particle from 90Y. Many investigators feel that the combination of the two may turn out to be the most effective form of PRRT for patients with non-operable NETs. Patient-specific dosimetrically determined levels of administered activities are being studied in an attempt to improve efficacy and reduce toxicity.

References:
Nuclear Medicine and $^{177}$Lu-DOTATATE Therapy: A Guide to Success

High-quality patient care and safe delivery of $^{177}$Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) within a nuclear medicine division begins with proper departmental and institutional preparation and multidisciplinary collaboration. Unlike other radiotherapies, $^{177}$Lu-DOTATATE PRRT administration at the Dana-Farber Cancer Institute (DFCI) involves teamwork among multiple groups, including nuclear medicine (technologists, nurses and physicians), radiation safety, pharmacy and members of the Gastrointestinal Cancer Center (GCC) clinic. It also requires the intravenous administration of amino acids and anti-emetics, close patient observation and care for managing side effects, and radiation safety preparation and monitoring. At DFCI we have established workflows and procedures that allow us to provide full outpatient care—including therapy—within a confined space in the nuclear medicine division.

In preparation for our participation in a $^{177}$Lu-DOTATATE PRRT Phase III clinical trial, much time was spent on a thorough review of the protocol, several meetings with key personnel and numerous emails with the study sponsor. In fact, based on our prior experience in a clinical trial testing a different radiotherapeutic tracer, we modified the protocol’s suggestions for dose delivery and chose to draw the $^{177}$Lu-DOTATATE dose from a vial to a syringe and administer the treatment via a shielded Graseby pump. This interaction enabled us to successfully establish multidisciplinary training procedures and workflows needed to deliver the treatment.

As the lead imaging research technologist, my role was to ensure that all team members understood the protocol and received the required training. In addition to the sponsor-required protocol training, the team underwent training in workflow, radiation safety, administration of amino acids and anti-emetics, preparation and administration of $^{177}$Lu-DOTATATE, medication management, usage of the Alaris and Graseby pumps and patient care. I also centralized the ordering procedure of the $^{177}$Lu-DOTATATE dose and served as a communication liaison between all groups to coordinate patient and staff scheduling, medication ordering and receipt, and departmental preparation.

Based on the experience that we acquired with this Phase 3 trial, I was encouraged to write an Operations Manual for $^{177}$Lu-DOTATATE administration in a nuclear medicine division. This manual provides multidisciplinary guidance for all operational procedures involved in the delivery of $^{177}$Lu-DOTATATE PRRT and summarizes the roles, responsibilities and recommended training for each group; required human and physical resources; and procedures for departmental preparation, dose preparation and administration. Our team hopes to publish the manual as guidance for other nuclear medicine departments interested in delivering this novel therapy safely and successfully in their setting. Given that the results of the trial have now been published and the drug is pending FDA approval, it would be timely for your department and institution to plan a multidisciplinary collaboration to establish the workflows and procedures needed for safe delivery of PRRT to your patients.

Reference:

WHAT’S HAPPENING

CTN Announces New Anatomy Webinar Series

Courtney Lawhn Heath, MD, and Shyanne Mortimer, CNMT

The SNMMI Clinical Trials Network (CTN) is pleased to present a new Anatomy Review Webinar Series. If we understand the anatomy we are imaging, we can produce better images. Aimed at nuclear medicine technologists and organized by body region, this series emphasizes key anatomical structures and their appearance on commonly performed nuclear medicine exams. In some cases, it will also help you stay current by covering newer research agents. Presented by physicians and experienced technologists, the series covers the areas noted below. Check the CTN website for the final dates in 2018.

CTN ANATOMY REVIEW SERIES

Anatomical Area: Head and neck
Speaker: Michael Graham, PhD, MD

Anatomical Area: Brain
Speaker: LisaAnn Trembath, CNMT, MSH, CCRA, FSNMTS

Anatomical Area: Chest and lungs
Speaker: Robert Flavell, MD, PhD

Anatomical Area: Abdomen
Speaker: Christopher Sakellis, MD

Anatomical Area: Male and female pelvis
Speaker: Courtney Lawhn Heath, MD
Adapting to GE’s First Prototype PET/MR Scanner and Research Imaging

Transcending from the role of clinical nuclear medicine technologist to the role of pioneer PET/MR research technologist was exciting and full of new challenges. Actually, the adjectives solitary, intimidating, fulfilling and career-changing would be more appropriate!

In December 2013, GE installed its first prototype PET/MR scanner at Stanford University. It didn’t have a name, and there was debate about whether it should be called MR/PET or PET/MR, highlighting the divide between radiology and nuclear medicine. My role at Stanford encompassed not only operating this new scanner but also establishing the PET/MR research department, collaborating with GE engineers through prototype iterations, and collaborating with new teams of researchers and clinical research coordinators to launch new PET/MR studies. This experience quickly led to expansion beyond my Stanford University role. With the advent of PET/MR, it has become important to bring researchers, physicians and technologists from across the globe together to discuss experiences and challenges. Issues—including workflow and development of clinical applications—can best be addressed with open communication. In the United States, two new meetings have been organized to further this goal: the PET/MR User Group Meeting and the International Society for Magnetic Resonance in Medicine/SNMMI PET/MR Workshop.

PET/MR hybrid technologists are still a small and specialized group. Identifying peers and establishing open dialogue is necessary to navigate this new hybrid technology and pave the way for future technologists. When I accepted the position of PET/MR research technologist, little did I know just how encompassing this role would be. I have encountered many questions, still unanswered, that continue to impact our field. This has encouraged me to be more involved: to collaborate, network and teach others.

From my new perspective, I feel very fortunate to work in an exciting field that is ever-evolving and changing our understanding of medicine and treatment of disease. I encourage my fellow technologists to also expand their roles and help sculpt the future of research and diagnostic imaging.

The Common Rule Undergoes Revisions

Protection of human subjects in research is rooted in three core beliefs: autonomy, justice and beneficence. These ethical tenets were translated into law in 1991 in the Code of Federal Regulations (45CFR§46), referred to as “The Common Rule,” and 15 federal agencies and departments have adopted them. The Common Rule has remained unchanged since its initial draft despite significant advances in certain areas of research such as functional imaging, genetics and electronic medical records.

In January 2017, the U.S. Department of Health and Human Services (DHHS) issued notification of an update to The Common Rule to be implemented in January 2018. Primary revisions focus on privacy and safety issues. The changes address Institutional Review Board policies and procedures but impact all human subjects research. A few key changes to note include:

- **Identifiable** is now a term subject to change. With increasing genetic assays, web-publishing and personal computing power, it is not unrealistic to think that a person could be identified by their genetic code. For this reason, a panel of experts will convene no less than once every four years to evaluate technologic evolution and its impact on privacy.

- Changes to waived-consent research impact medical research significantly. Institutional review boards (IRBs) are allowed to provide consent waivers for only those individuals who have not declined broad consent for research purposes. The broad consent is a tool fundamentally waiving the Health Insurance Portability and Accountability Act (HIPAA) for research purposes. If offered, and a patient declines, the patient’s data must not be used for any consent-waived research (commonly termed retrospective research or chart review research).

There is rumor that the revisions to The Common Rule will be delayed until January 2019, but this has not yet been confirmed. In preparation for the changes when adopted, it is wise to reach out to your IRB of record now to ask how your research workflows will be impacted.
Timing IS Everything: Our Experience with Axumin

Introducing any new agent and imaging protocol into a busy nuclear medicine department creates many challenges. Our experience with 18F-fluciclovine (Axumin™) was no exception. This radioactive diagnostic agent (initial U.S. approval 2016) is indicated for PET imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. A national radiopharmacy network oversees production of Axumin and must be called 48 hours prior to the planned date of utilization. At the current time, isotope production and delivery for our facility is available only on Thursdays after 12 noon. The local radiopharmacy capable of synthesizing 18F-fluciclovine receives the byproduct from the manufacturer and transfers the final product directly to the nuclear medicine department.

Our nuclear medicine department is quite large, and we perform a wide variety of nuclear imaging procedures every day. This experience has helped to define four key areas where timing is critical to ensuring acquisition of high-quality images for physician interpretation and enhancing outcomes by improving patient experience. Good communication with the patient throughout the process is very important.

- **Scheduling**—Once insurance payment has been approved, the patient is scheduled for the scan, and Axumin is ordered. Patients are given directions to the hospital and the department as well as precise preparation instructions.
- **Preparation**—The patient is instructed to refrain from eating and drinking (except water to take medications) at least four hours prior to the scan and to refrain from any strenuous physical activity for two days prior to the appointment. Muscle uptake from exercising or muscle strain can interfere with scan interpretation.
- **Injection**—Once prepared for the injection and on the imaging table, a scout view is performed and the limits of acquisition are set. The dose of Axumin is assayed in a radioisotope dose calibrator immediately prior to injection. The patient is then injected in the right arm (both arms down) over a period of 5 seconds, unless contraindicated. As soon as the injection is completed, the remaining dose is assayed to determine residual activity. The net activity is then entered into the imaging system.
- **Imaging**—Imaging begins 3 to 5 minutes post-injection. Any delay in imaging can degrade the image quality. The entire imaging procedure takes 25 to 30 minutes. We preset a specific imaging protocol for using 18F-fluciclovine into our time-of-flight PET scanner to ensure reproducibility.

Since August 2016, we’ve performed studies on patients from across the United States and Canada. In our experience, results with Axumin have been very positive, producing excellent correlation between scan results and the patient’s clinical condition. The entire process—from scheduling to imaging—is successful only if the timing of all events and procedures is carried out in the required manner.
CTN Offers Services for Academic Clinical Research

The SNMMI Clinical Trials Network offers a variety of services to assist academic investigators with their clinical research.

- Trial design using PET imaging
- Protocol and study document development
- Reader training for new radiopharmaceuticals
- Expert analysis of PET images
- Scanner validation and QC troubleshooting
- IND/ANDA preparation for FDA review
- Access to information on investigational PET agents for use in clinical trials

Contact CTN for more information at ctnadmin@snmmi.org.

Save the Dates

Third AACR-SNMMI Joint Conference on State-of-the-Art Molecular Imaging in Cancer Biology and Therapy
February 14–17, 2018 • San Diego, CA

39th Annual High Country Nuclear Medicine Conference
March 3–7, 2018 • Sun Valley, ID

ASNC Nuclear Cardiology Today 2018
April 20–22, 2018 • Chicago, IL

12th Congress of the World Federation of Nuclear Medicine and Biology
April 20–24, 2018 • Melbourne, Australia

2018 ASCO Annual Meeting
June 1–5, 2018 • Chicago, IL

SNMMI 2018 Annual Meeting
June 23–26, 2018 • Philadelphia, PA

54th DIA Annual Meeting 2018
June 24–28, 2018 • Boston, MA

WMIC 2018 – World Molecular Imaging Congress
September 12–15, 2018 • Seattle, WA

European Association of Nuclear Medicine (EANM18)
October 12–17, 2018 • Dusseldorf, Germany

RSNA 104th Scientific Assembly and Annual Meeting
November 25–30, 2018 • Chicago, IL

Editorial Committee
David Dick, PhD
Courtney Lawhn Heath, MD
James Mountz, MD, PhD
Jonathan McConathy, MD, PhD
Jonathon Nye, PhD
John Sunderland, PhD, MBA
Colin Young, MD
Bonnie Clarke, BS
Shyanne Mortimer, CNMT

Issue Editor – David Dick, PhD
Managing Editor – Tina Kiss
Graphic Designer – Laura Reyes