The DOTA Discussion: TOC, TATE and NOC

Michael Graham, PhD, MD, Ronald Walker, MD, FACNM, and David Dick, PhD

The $^{68}$Ga-radiolabeled somatostatin receptor ligands, DOTATOC, DOTATATE and DOTANOC, have been used to image neuroendocrine tumors (NETs) clinically in Europe for almost a decade. The image quality of these agents is significantly better than the currently US-approved agent, $^{111}$In-Octreotide. Development of these agents in the United States has lagged due to uncertainty regarding the intellectual property associated with the three ligands and questions regarding precursor availability. In addition, there has been uncertainty regarding which of the three ligands should be focused on for development in the United States, with no clear way to determine which, if any, is best.

Currently, the University of Iowa, Vanderbilt University and Indiana University are studying NET patients with DOTATOC, DOTATATE and DOTANOC, respectively. These sites are performing studies under investigational new drug (IND) authorizations with “cost recovery,” which allows billing for the cost of the DOTA synthesis; reimbursement for the imaging portion of the study is beyond the purview of the US Food and Drug Administration. The three agents are similar in that they all are useful for imaging NETs, but there are also differences, particularly in their receptor affinity for the different somatostatin receptor (SSTRs) subtypes.

$^{68}$Ga-DOTATOC primarily targets SSTR2, but also SSTR3 and SSTR5, and has been used clinically in Europe for almost a decade. It has proven to be particularly useful in the evaluation of patients who may be candidates for peptide receptor radionuclide radiotherapy (PRRT) with $^{90}$Y-DOTATOC or $^{177}$Lu-DOTATATE. It has also been used in the diagnosis and staging of NETs (most commonly carcinoid) and in the localization of primary tumors in patients with multiple liver metastases from an unknown primary.

At the University of Iowa, we are using $^{68}$Ga-DOTATOC positron emission tomography/computed tomography (PET/CT) in an active clinical trial (NCT01619865, www.clinicaltrials.gov) to test its efficacy, diagnosis, staging and measurement of response to treatment in patients with SSTR-positive tumors. An approximate enrollment of 200 patients is anticipated during a three-year time period, with over 100 patients already having been imaged.

The DOTA Discussion. Continued on page 2
Ron Walker, MD, FACNM

$^{68}$Ga-DOTATATE is an almost exclusive SSTR2 receptor ligand. Vanderbilt University has an ongoing clinical trial (NCT01396382, www.clinicaltrials.gov) for imaging patients with SSTR-expressing tumors for staging and to search for an unknown primary. The initial trial is for 100 patients (70 accrued to date) who also undergo toxicity testing with baseline blood tests, vital signs, pulse oximetry and 12-lead EKG repeated after injection of $^{68}$Ga-DOTATATE. The first 70 patients have shown no toxicity. The scans are interpreted by two nuclear medicine physicians independently and blinded to other imaging results. The results are analyzed on a “per-patient” basis since it is not possible to obtain biopsy or follow-up on every individual lesion. Impact on care is compared to conventional imaging ($^{111}$In-Octreotide imaging, CT, magnetic resonance imaging and/or $^{18}$F-FDG PET/CT). A trained neuroendocrine surgeon then assesses for impact on care from the added $^{68}$Ga-DOTATATE PET/CT compared to conventional imaging alone.

From the first 70 patients, 41 (59 percent) had no change in care, 9 (13 percent) had a minor change in care (usually a change in surgical plan for patients already scheduled for surgery) and, importantly, 20 patients (29 percent) had a major change in care (usually cancellation of surgery for patients previously thought to be candidates for attempt at surgical extirpation but found to be inoperable and referred for chemotherapy and/or PRRT). Thus, a total of 29 patients (41 percent) had a change in treatment based on the $^{68}$Ga-DOTATATE PET/CT scan. Very importantly, about one-third of patients had cancellation of futile surgery.

$^{68}$Ga-DOTANOC is a conjugate of the somatostatin analogue 1-Nal3-octreotide (NOC) and $^{68}$Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). The somatostatin analogue NOC has a high affinity for SSTR2, SSTR3, and SSTR5; these receptor subtypes have been shown to be present in large numbers on NETs and their metastases, while most other normal tissues express low levels of these SSTR subtypes. In a recent study reported in Aunt Minnie (2011), DOTANOC PET/CT findings established true positives for primary tumors in 54 patients and true negatives in 37. Three patients had false positives and 15 had false negatives. The scans localized primary tumors in 18 patients with carcinoid, 15 patients with gastrinoma, four patients with insulinoma, and 17 patients with NETs not otherwise specified. DOTANOC PET/CT also was able to detect metastases in 75 (97 percent) of 77 patients with one or more sites of metastases, with the hybrid modality finding a total of 106 metastatic regions among the 75 patients. The most common site of metastases was the liver, followed by the lymph nodes. Once again, DOTANOC PET/CT achieved sensitivity, specificity, positive predictive value, negative predictive value, and accuracy equal to or greater than that of conventional imaging. There were true-negative results in 32 patients and no cases of false-positive lesions. Two patients had false-negative results for liver metastases. DOTANOC PET/CT appears to be a highly sensitive and specific modality, and is better than conventional imaging, in the detection of gastroenteropancreatic NETs. In addition, a negative finding on DOTANOC PET/CT can guide the treating physician to choose an alternate form of treatment.

Reference: Naswa et al. AJR, Vol. 197:5, pp. 1221-1228

The DOTA Discussion. Continued from page 1.

David Dick, PhD

$^{68}$Ga-DOTANOC fused PET/CT (above) and anterior 3D MIP (right) images of a patient referred for possible surgical extirpation of a NET with known metastatic disease to the liver. The $^{68}$Ga-DOTATE PET/CT images reveal previously occult metastatic disease in the mediastinum (arrows), indicating that the patient was not a candidate for surgical cure. This patient was referred for alternate treatment and spared an extensive, futile surgical procedure as a result of the $^{68}$Ga-DOTATE scan compared to conventional imaging.

The DOTA Discussion. Continued on page 3.
Message from the Co-Chairs

SNMMI’s Clinical Trials Network (CTN) has made great strides to help advance the development and use of molecular imaging biomarkers in clinical research. Initial charges set forth for the CTN committees have evolved over the past four years to meet the dynamic needs of the molecular imaging community and to address changes in the national and global regulatory arena for conducting clinical research. We take this opportunity to highlight some key accomplishments and update the community on our activities.

Michael Graham, PhD, MD
John Hoffman, MD

CTN Updates

Database Committee
Chair: John Sunderland, PhD

CTN’s comprehensive web-accessible database provides tools to store and manage the imaging and production sites registered under the CTN. Through its Database Reporting Tool (DaRT), CTN provides industry partners with access to accurate and current information on registry sites, including an extensive listing of radiopharmaceuticals and radionuclides manufactured at academic institutions and commercial facilities. It includes refined capabilities to search for qualified PET manufacturing centers in geographical areas, what they produce and how often, as well as qualified imaging sites for use in multicenter trials. Recently, the ability to generate and print reports has been added to the database, enhancing its functionality and expanding its initial goals. This committee continues to manage the database’s day-to-day activities, review requests from industry and CTN members for additional features and implement the necessary updates as they arise.

Phantom Program and Scanner Validation Committee
Chair: Paul Christian, CNMT, BS, PET

The Scanner Validation Committee, under the CTN’s Phantom Program, has successfully validated over 215 PET/CT scanners worldwide using the CTN chest oncology phantom. Because this unique phantom has the characteristics of a clinical simulator, the exercise evaluates both the performance capabilities of the scanner and the imaging personnel’s ability to follow instructions and the assigned tasks. Many of these validated scanners have been used in studies with CTN partners as a means to help standardize images obtained in drug development studies. Two versions of the chest oncology phantom are now in circulation, with one version having slightly different lesion locations to further challenge sites undergoing revalidations. A third version was developed for sale to industry and research groups for testing purposes and to help develop a standardized imaging protocol for use in clinical trials. CTN also has developed a brain phantom and a cardiac phantom, both able to be modified to meet study-specific needs.

Centralizing the activities of this committee is the use of the Keosys Imagys™ (France) platform, a secure program that facilitates image review and data management. Industry partners and their designated imaging contract research organizations can view the images and download them to their own servers for further analysis. This server has greatly streamlined the image review process to better meet study start-up requirements as well as ongoing revalidations.

In summary, we have emerged from the past period of indecision and are beginning to move towards regulatory approval of ⁶⁸Ga-radiolabeled SSTR ligands, making a considerable positive impact in the management of patients with NETs. While trials are moving forward with all three agents, widespread use of these agents in the United States may be determined by their patent expirations (2014 for DOTATOC, 2015 for DOTATATE, 2022 for DOTANOC). CTN is coordinating the efforts at sites holding a current IND for these agents, as well as several other sites that are developing the capability of doing similar studies. An important goal is to collect the imaging and safety data in a consistent way that facilitates its presentation to the FDA for final approval. The path forward involves applying for Orphan Drug Status for these agents followed by planning and executing a small, multi-center confirmatory clinical trial.

The DOTA Discussion. Continued from page 2

CTN Updates. Continued on page 7.
Funding Proposal Submitted

anti-[18F]FACBC Imaging for Prostate Cancer: Pathway to Approval through Movember

John Sunderland, PhD

SNMMI’s Clinical Trials Network (CTN) has organized an international coalition of nine academic sites to perform a phase III multi-center clinical trial aimed toward final regulatory approval of anti-[18F]FACBC (anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid) for use in prostate cancer. This effort is in response to a large funding initiative by the Australian-based men’s health advocacy group, Movember (http://au.movember.com), which has committed $5 million to largely test late-phase novel imaging agents in advanced prostate cancer patients. The proposed project combines the resources of the CTN with five US-based academic sites (University of Iowa, University of Utah, Emory University, Washington University and Massachusetts General Hospital) and international researchers from the University of Bologna, the Technical University of Munich, Peter MacCallum Cancer Centre (Melbourne) and The Royal Marsden Hospital in London.

anti-[18F]FACBC is a synthetic amino acid analog PET radiotracer and has shown excellent promise in staging and restaging patients with prostate cancer (see Biomarker Spotlight in this issue). Two phase II clinical trials have demonstrated that PET/CT imaging with anti-[18F]FACBC, is highly sensitive and specific in the detection of metastatic prostate cancer, particularly in lymph nodes, and shows great promise to perform this task significantly better than other methods presently available. This coalition’s primary objective is to get anti-[18F]FACBC approved for clinical use to identify lymph node involvement in prostate cancer by submitting a new drug application (NDA) to the Food and Drug Administration and its sister organizations worldwide, and to generate enough comparative effectiveness data to support positive coverage decisions in as many regions of the world as possible.

If funded, CTN will play a central role in the clinical trial’s execution through its established infrastructure to:

- validate all PET/CT scanners used within the trial via its Phantom Imaging Program;
- use its Keosys Imagys server for secure networked study image storage and analysis;
- help design and implement the detailed clinical trial design;
- administer a multi-site IND for anti-[185F]FACBC; and
- offer clinical trial-related educational support for staff at participating institutions.

This coalition is hopeful that some level of funding will be achieved, with the project launching as early as July 2013.

What’s Happening

Focus on the CTN Intern: Lance Burrell, MS, CNMT, ARRT(CT)

We are very pleased to welcome Lance Burrell, MS, CNMT, ARRT(CT), as the CTN intern for 2013-2014.

In his intern application, Lance stated that, “The pursuit of professional fulfillment is a life-long and complex journey.” Currently employed at the Huntsman Cancer Institute at the University of Utah, Lance pursues his journey by working in a busy academic environment where clinical research is a major aspect of his day-to-day responsibilities. In line with these duties, Lance will spend part of his internship helping to refine methods and practices in improving quality and consistency in research imaging. As a CTN intern, his goal is to learn from the vast experience and knowledge of those currently in leadership roles within the CTN and SNMMI and to increase his ability and value in mentoring future young professionals.

CTN Collaborates with the Pediatric Brain Tumor Consortium

Frederic H. Fahey, DSc, Children’s Hospital Boston, and Tina Young Poussaint, MD, Harvard Medical School

The Pediatric Brain Tumor Consortium (PBTC), which was formed by the National Cancer Institute in 1999, is devoted to the study of correlative tumor biology and new therapies for primary CNS tumors of childhood. PET imaging is incorporated into many PBTC protocols, with approximately 550 PET scans having been done during the past 10 years. Under the guidance of Tina Young Poussaint, MD, director of the PBTC’s Neuro-Imaging Center, the group evaluates new treatment response criteria and neuro-imaging methods to understand response to therapy. Frederic H. Fahey, DSc, SNMMI president, works closely with her on these important projects. During the past 10 years, the 11 PBTC study institutions have performed two different phantom quality control studies to better evaluate the quality of the PET study data collected, and subsequently published a paper (Med. Phys. 37(7), July 2010). The group now plans to collaborate with the CTN to see how well the sites, with varying levels of physicist support, image CTN’s unique brain phantom and analyze the results. The exact process for phantom scan, image upload and review and analysis is yet to be decided, but it is anticipated that all study sites will have completed the CTN brain phantom scanner validation by fall of 2013 when the current grant has its next review.
Prostate cancer is the second leading cause of cancer death in men and is expected to account for almost 30 percent of new cancers in men in the United States in 2013. Accurate detection and staging are critical for optimal treatment planning. Current techniques such as routine CT and MR, or commercially available molecular imaging agents, such as $^{18}$F-FDG (a glucose analogue) and $^{111}$In-capromab pendetide (a monoclonal antibody to prostate specific membrane antigen, PSMA), have limited diagnostic accuracy in prostate cancer. Therefore, better imaging biomarkers are needed.

The non-natural amino acid, \textit{anti-1-amino-3-}$^{18}$F-fluorocyclobutane-1-carboxylic acid (FACBC), targets increased amino acid transport in prostate cancer and has shown promising results in initial clinical trials (1, 2). Unlike most radiolabeled amino acids, $^{18}$F-FACBC undergoes relatively little renal excretion which avoids high levels of radioactive urine in the bladder which could interfere with detection of prostate cancer in the gland itself and in pelvic lymph nodes. Recent studies suggest that the uptake of $^{18}$F-FACBC by human prostate cancer cells is mediated by both LAT1 and ASCT2 amino acid transporters, both of which are over-expressed in a wide range of human cancers (3, 4).

In phase II trials, $^{18}$F-FACBC-PET/CT has shown higher sensitivity and specificity than $^{111}$In-capromab pendetide and conventional imaging for detection of prostate cancer in the prostate bed as well as in regional lymph nodes (1).

Rapid uptake in tumor allows imaging as soon as 10 min after $^{18}$F-FACBC-PET/CT injection with relatively high target to background ratios. Current efforts are focused on validating $^{18}$F-FACBC in larger patient populations, particularly in men with evidence of biochemical recurrence based on rising serum prostate specific antigen (PSA) after definitive surgical or radiation therapy.

References:


**Figure 1.** Recurrent prostate cancer in the prostate bed. Sagittal $^{18}$F-FACBC-PET (A) and fused $^{18}$F-FACBC-PET/CT (B) images after patient underwent radical prostatectomy, now with serum PSA of 16.9 ng/mL and suspicious for recurrence. The white arrows demonstrate focally-increased FACBC between the rectum and bladder, subsequently proven to be recurrent prostate cancer. \textit{Figure adapted with permission from reference 1.}

**Figure 2.** Lymph node metastasis. Axial $^{18}$F-FACBC-PET (A) and fused $^{18}$F-FACBC-PET/CT (B) images after patient underwent radical prostatectomy, now with serum PSA of 1.1 ng/mL. The white arrows demonstrate focally-increased FACBC in a left pelvic lymph node measuring 5 mm in short axis and was subsequently proven to be recurrent prostate cancer through biopsy. \textit{Figure adapted with permission from reference 1.}
Tech Talk: A NMT as an Imaging Analyst – Yes, You Can!

Adam Opanowski, CNMT, PET, NCT, RT (N), Imaging Analyst, American College of Radiology Imaging Core Laboratory, American College of Radiology Clinical Research Center, Philadelphia, PA.

My career path to my current position as an imaging analyst began as a staff nuclear medicine technologist (NMT) at the Hospital of the University of Pennsylvania where I was fortunate to be involved in clinical research. Seeing how clinical trials have the potential to positively affect patient care was very rewarding. This experience led me to join the American College of Radiology Imaging Core Laboratory (core lab) as an imaging analyst where I primarily provide support for the multicenter clinical trials conducted by the American College of Radiology Imaging Network (ACRIN).

The core lab provides the infrastructure for comprehensive image management and analysis activities within a clinical trial that seeks to answer important scientific questions about the role of imaging in improving patient care. For example, ACRIN recently completed patient enrollment for a study (ACRIN 6688) evaluating whether PET scans using the investigational radiotracer FLT can determine early on in the course of breast cancer chemotherapy whether the therapeutic treatment is actually benefitting the patient. As the imaging analyst for this trial, I was able to draw upon my previous NMT clinical research experience and use the core lab tools to carry out the image quality assurance functions, including managing the site qualification process to ensure sites could reliably produce quality FLT-PET scans; reviewing images to confirm they adhere to the protocol specifications; and working with NMTs around the country to solve any imaging issues that arose at their sites. The researchers are now “crunching the numbers” to prepare a paper for publication in a scientific journal announcing the trial’s results.

One very exciting aspect of my position as an analyst is the opportunity to work with leading imaging researchers on the development of protocol specifications for advanced imaging methods, e.g., kinetic modeling of dynamic PET data. It’s very inspiring to see, firsthand, how current nuclear medicine imaging research has the potential to be part of routine clinical practice in the future.

I encourage NMTs interested in cutting-edge imaging to consider a career opportunity in research—you can be an imaging analyst too!

Research Essentials: GCP in Clinical Research

Excerpt from CTN Course 103

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human patients. GCPs are published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and cover all aspects of clinical trials. A variety of other organizations—in the United States and throughout the world—also oversee how clinical research should be carried out to ensure that the rights, safety and well-being of trial patients are protected and clinical trial data are reliable.

Within the four overriding ICH sections, Efficacy (publication number E6) is the most relevant guideline affecting clinical research practices, and all personnel must be familiar with this document. In the United States, the Code of Federal Regulations (CFR) assists clinical researchers, sponsors and drug manufacturers in complying with GCP. Key regulations include:

- 21 CFR 312: Requirements for an Investigational New Drug
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 56: Institutional Review Boards

If you follow ICH Guidelines for GCP, you practice a more stringent form of good clinical practice during the study.

Read and understand both sets of guidelines to provide the best possible care to your study patients and the most credible data to the study sponsor.

Tech Tip

Adhere to the Acronyms!

- ICH: International Conference on Harmonisation
- GCP: Good Clinical Practice
- FDA CFR: Food and Drug Administration Code of Federal Regulations
- OHRP: Office of Human Research Protection
CTN Updates. Continued from page 3.

Site Orientation and Education Committee
Chair: Marybeth Devine, CNMT, BS, RT

In keeping with its original key charge, the Site Orientation and Education Committee develops and maintains a comprehensive selection of courses with a focus on performing high-quality molecular imaging in research studies. Topics range from basic clinical research “how-to’s” to more advanced subjects such as scanner quality control and image standardization methodology. A set of five “core courses” cover the key elements of clinical research and, along with recorded webinars, meeting presentations, and other lectures on research-related areas, are available on the SNMMI website. Most offer CE credit for physicians and technologists for a very reasonable fee. In addition to the CTN curriculum, this committee develops clinical research-related offerings for the SNMMI Annual and Mid-Winter Meetings and often works with the SNMMI-TS and SNMMI Radiopharmaceutical Sciences Council to jointly present on timely and important topics. It also identifies opportunities for outside presentations, such as at the annual Drug Information Association meetings. Developing these diverse educational channels benefits imaging sites, industry sponsors and the molecular imaging community as a whole, as they create a global atmosphere of striving to achieve the highest quality of imaging possible in clinical research.

CTN Updates. Continued on page 8.

Acronyms are everywhere in clinical research. ICH and GCP are worldwide guidelines providing key standards that govern clinical research activities. In addition to those regulating US-based clinical trials, there are acronyms for specific clinical research directives in the European Union, Canada and other countries. Following the principles and regulations that ALL these acronyms represent is paramount to being a great research site!

CTN Hosts Categorical and CE Sessions

Join us for these outstanding educational offerings at the SNMMI 2013 Annual Meeting in Vancouver, British Columbia, Canada. In addition to its categorical and CE session, CTN continues its collaboration with the SNMMI-TS by presenting two joint CE sessions on unique clinical research imaging topics, with an international focus.

Saturday, June 8:    CTN Categorical: Challenges of Regulatory and Reimbursement Approval for Molecular Imaging Agents

Monday, June 10:   CTN/SNMMI-TS CE Session: What You Didn’t Know about Clinical Research

Tuesday, June 11:   CTN CE Session: The DOTA Debate
CTN/SNMMI-TS CE Session: Clinical Research in Canada: The Tech Experience

Don’t miss these outstanding sessions!

Clinical Trials Network
2013 WEBINAR SERIES

Be sure to catch the remaining 2013 webinars!

JUNE 20
PET QC: Optimizing Scanner Performance; John Sunderland, PhD

AUGUST 8
RECIST and Other Tumor Response Measurement Criteria; Heather Jacene, MD

OCTOBER 17
Optimizing Amyloid Imaging in Clinical Research; Satoshi Minoshima, MD, PhD

DECEMBER 12
Artifacts in PET Imaging: Examples and Explanations; Paul Christian, CNMT, BS, PET, FSNMMI-TS

CTN is also pleased to announce several of the proposed topics for its 2014 webinar series:
• PET/MR: Is It Ready for Prime Time?
• PET Imaging of the Brain: A Technologist’s Guide
• The RDRC and RSC: Their Role in Clinical Trials

Radiopharmaceutical Manufacturers Committee
Chair: David Dick, PhD

Initially titled the “Manufacturer’s Registry Committee,” the Radiopharmaceutical Manufacturers’ Committee’s name was changed in June 2012 to better reflect its revised goals and activities. Manufacturing sites participating in a trial using CTN resources are monitored by this committee. Its role is to ensure compliance with current regulatory guidelines, perform audits of study sites and work on a higher lever with industry partners to address unmet needs from the radiopharmaceutical manufacturing community.

Site Validation and Monitoring Committee
Chair: James Mountz, MD, PhD

The Site Validation and Monitoring Committee performs the critical role of gathering a variety of information on imaging facilities to assess their ability to successfully participate in multicenter clinical trials. A set of questionnaires elicits critical information on a site’s imaging capabilities, research infrastructure and personnel’s expertise in the use of both clinically-approved and investigational molecular imaging agents. After reviewing the site’s information in the CTN database and any other relevant information, the committee makes a determination for full “CTN Site Qualification” status. The committee also monitors site performance during the course of a study to ensure the imaging protocol is being followed.

Trial Design Committee
Chair: Jeffrey Yap, PhD

A primary goal of the Trial Design Committee is to help develop standardized imaging protocols for use in multicenter clinical trials. Committee members have expertise in oncology, neurology and cardiology studies, as well as regulatory requirements, and are able to assist sponsors in writing imaging protocols for new therapeutic agents or to test and validate new imaging approaches. Collaborations with other imaging groups have been successful in developing a protocol for FDG, not as a centralized investigational new drug (IND), but as a template with uniform guidelines that sponsors/sites around the world can follow for their own studies. Additionally, the committee is responsible for developing protocols for SNMMI CTN centralized INDs, such as the FLT IND, that sponsors can cross-reference in their trials. Plans to submit centralized INDs for other investigational agents are underway for 2013/2014.