PET Imaging of Immunotherapy

Anthony F. Shields, MD, PhD; Anna M. Wu, PhD; and Paula M. Jacobs, PhD

Immunotherapy has become one of the most active and exciting areas in oncology research and therapy in the last few years. This journey has incubated for over 100 years with efforts using a wide variety of potential therapies, beginning with Coley's toxins in 1891. The scientific maturation of monoclonal antibodies, first produced by Köhler and Milstein in 1975, has been instrumental in the clinical movement in immunotherapy. This led to the development of a growing number of anti-tumor antibodies, beginning with the FDA approval of rituximab (Rituxan®) for lymphoma in 1997. Antibody drug conjugates (ADC) were subsequently developed, such as brentuximab vedotin (Adcetris®), which was FDA-approved for lymphoma in 2011. Many other cytotoxic antibodies have been developed and approved, and a growing number are now in clinical trials.

The most recent research and clinical studies work to develop agents that stimulate the immune system rather than being directly cytotoxic. These have included antibodies that target “checkpoints” used to turn on and off the immune reaction to cancer. Using the infusion of activated immune T-cells and dendritic cells is also rapidly expanding, while anti-tumor vaccines continue to be an active area of research.

Three immune checkpoint inhibitors have been approved in the United States (US) including ipilimumab (Yervoy®), an antibody against the T-cell receptor CTLA-4, approved for use with advanced melanoma in 2011. D-1 is a protein found on the T-cells and binds to PD-L1 on tumor cells impairing the immune response. Pembrolizumab (Keytruda®) and nivolumab (Opdivo®), treatments that target PD-1, were approved for use in melanoma in 2014, and for non-small cell lung cancer and renal cancer in 2015.

A number of other antibodies against both PD-1 and PD-L1 are in development for a wide variety of cancers, either when given alone or combined with chemotherapy, radiation or other immune modulators. In the treatment of advanced melanoma, antibodies against CTLA-4 and PD-1 have been combined and found to have a 60 percent response rate, with over half of the patients alive at two years. Infusions of T-cells directed against tumors have particular promise in early trials in lymphoma and leukemia and are being tested against solid tumors.

T-cells have been genetically engineered to express chimeric antigen receptors (CAR-Ts) directed at the tumors. Others have developed T-cells that are mixed in the lab with bispecific antibodies where one arm binds to the tumor cell and the other to the T-cell (bispecific armed T-cells; BATs). Work is also being done with bispecific T-cell engaging antibodies, such as blinatumomab (Blincyto®; approved to treat acute lymphocytic leukemia), directly injected into the patient. Finally, a number of promising vaccine trials are using parts of cancer cells or pure antigens.

The ultimate success of immunotherapies will be measured by demonstrating improved patient survival, but waiting for such an assessment may take a long time. In the meantime, subsequent treatment can confound the evaluation. While immunotherapy has demonstrated activity in some patients, as measured by treatment response and improved survival, most cases to date report that only a limited number of patients appear...
to benefit. Investigators continue to seek improved predictors of response prior to initiation of therapy. For example, tumor expression of PD-L1 has been found to predict response of pembroluzimab in patients with lung cancer, but it is not a very robust marker. Patients with tumor cells positive for PD-L1 of 1-49 percent had an overall response rate of 50 percent compared to those with expression of 50 percent, respectively.2

Even more problematic is the assessment of response after the start of treatment. Investigators often see patients develop an inflammatory response after initiating checkpoint therapy, which leads to increases in size of known lesions and the appearance of new lesions on imaging scans. In some of the early immunotherapy studies, such patients might be removed from the trials since they were judged to have progressive disease. Over the ensuing months, however, their cancer shrank or even disappeared completely. Figure 1. This led to the modification of the standard approach for assessing tumor response allowing for “pseudo-progression,” as described in the immune-related Response Evaluation Criteria in Solid Tumors (iRECIST). This assessment method still leaves much to be desired, however, and protocols regularly allow patients to continue on study despite apparent tumor growth if the treating clinicians judge it beneficial to the patient.

New imaging methods, clearly needed as predictive markers and to assess treatment response, are currently being developed and tested in some immunotherapy trials. Positron emission tomography (PET) tracers such as [18F]-Foscarnet (FDG) are regularly taken up in inflammatory cells, which is known to confound the use of FDG-PET and make it difficult to discern tumor uptake may signal response, and this approach is being tested in studies to determine if rapid increases in FDG retention may predict successful therapy.3,4 Non-invasive imaging of expression of PD-L1 could be of significant value for profiling tumors and potentially predicting responses to treatment with checkpoint inhibitors. Imaging using [18F]-FDG or [11C]-18F-Fluciclovine (F-AraG) has been shown to preferentially accumulate in activated T-cells and stromal cells in vivo.5 In a different approach, Somer et al. have introduced [22F]-2-deoxy-2-[18F]fluoro-D-arabinofuranosylcytosine ([18F]-FA-C) has been developed to assess activity of deoxyctydine kinase and is selectively accumulated in activated lymphocytes in the thymus, lymph nodes, and spleen, although the capacity to image tumor-infiltrating T-cells can be confounded by uptake in tumor cells in vivo. In a related approach, the guanosine analog 2'-deoxy-2'-[18F]fluoropyridoxyridine ([18F]-OMP) has been developed as a PET imaging tool for imaging PD-L1 in tumor-bearing mice.6

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CTN as a Catalyst for the MI Field

CTN667 hosted a workshop with the National Cancer Institute (NCI) on Monday, May 2, 2016, titled “Immunotherapy: Modulation, Therapy, and Imaging.” What can we do in clinical trials now? The goal of the workshop was to identify “shovel-ready” projects that could be added to clinical trials, either NCI- or industry-sponsored, by the end of 2016. In his welcome to the invited participants, the workshop chairman, Tony Shields, MD, PhD, said, “Immunotherapy clearly is the hottest topic in medical oncology today.” However, we have not been able to turn the evaluation of patients into a routine imaging strategy. As a result, we can only think of studies that use imaging strategies because of the time it takes to see a response in some patients. The assembled group of immunologists, imagers and industry representatives discussed imaging technologies beyond rRECIST (immunotherapy) that could be integrated into trials to measure response. Additionally, the group was charged with identifying markers that will predict the response of patients. The video webcast is available for viewing at CTNimmunotherapy.com and imaging.

Earlier this year, on February 29, CTN and SNMMI leadership held a three-hour meeting in Philadelphia with 20 representatives from imaging and medical societies primarily assisting with trial design and regulatory strategy. These discussions have definitely resulted in restructuring and accelerating the pathways toward FDA approval.

In the NEWS

Three Radioactive Agents on the Pathway Toward Approval

David W. Dick, PhD

Advanced Accelerator Applications (AAA) has announced a new drug application (NDA) filing plan with the U.S. Food and Drug Administration (FDA) for lutetium-177-[18F]-fluciclovine (NETSPOT), a radiolabeled somatostatin analog peptide for treating neuroendocrine tumors. AAA is also submitting a marketing authorization application (MAA) to the European Medical Association (EMA). Additionally, AAA initiated an expanded access program in the U.S. for lutetium. This program makes lutetium available to thousands of patients suffering from inoperable, somatostatin receptor-positive, midgut carcinoid tumors. Visit www.clinicaltrials.gov and access trial number NCT02705313 for more information on this program.

AAA has also filed an NDA with the U.S. FDA and an MAA with the European Medicines Agency (EMA) for nitrocryptate ([18F]-DOTA-labeled fluorine-18, [18F]-FDOTATOC) to be used for imaging and treatment of neuroendocrine tumors. [18F]-FDOTATOC is a somatostatin receptor-positive neuroendocrine tumor imaging agent. The product is intended for use in the functional diagnosis and management of patients with neuroendocrine tumors. [18F]-FDOTATOC received Priority Review from the FDA on June 1, 2016, the drug was approved. This is the first of its kind in the U.S., and its approval will impact the management of thousands of patients who have either had to travel internationally for imaging and treatment, or been a part of approved clinical trials at select sites in the U.S. Blue Earth Diagnostics (BED) has received approval for its [18F]-FDOTATOC (NETSPOT) for imaging and treatment of neuroendocrine tumors. BED opened a multicenter clinical trial of fluciclovine at six institutions in the United Kingdom for evaluation of the management of patients with recurrent prostate cancer. Fluciclovine potentially offers superior images over the currently approved radiopharmaceutical for this group of patients. The patients and the nuclear medicine community both benefit from having more approved radiopharmaceuticals. The CTN is excited to see three more radiopharmaceuticals heading towards approval and is available to assist others in their efforts to gain approval for radiopharmaceuticals under development.
Another promising target is the CXCR chemokine receptor 4 (CXCR4), which has been explored as a diagnostic target using a 64Cu-labeled small molecule and a 89Zr-labeled antibody in PET studies in tumor-bearing mice. In the latter case, use of a fully human antibody provides a potential therapeutic as well as a diagnostic agent. Turning to the immune cells themselves, an important target would be CD8+ cytotoxic T-cells, which are the subject of many current cancer immunotherapy approaches (e.g., checkpoint inhibitors, vaccines, bispecific antibodies). Tavaré et al. engineered murine CD8-specific small molecule fragments and demonstrated the ability to detect and image endogenous CD8+ T lymphocytes in normal mice. Importantly, this approach was recently extended to the detection of tumor-infiltrating lymphocytes in models of cancer immunotherapy, including treatment with an immunomodulatory antibody (anti-CD137/4-1BB), a checkpoint inhibitor (anti-PD-L1 antibody), or adoptive transfer of OT-1 T-cells in mice (Figure 4)15.

In summary, there are a large number of new immunotherapy approaches that have reached the clinic, and these are now being evaluated for a wide variety of tumors. One major limitation in both clinical trials and routine treatment of patients with such approaches is the difficulty in predicting which patients are likely to respond, and then monitoring those receiving therapy. So far, pathologic and molecular markers have helped, to some extent, in suggesting that certain tumors may find benefit from treatment, such as melanomas and mismatch repair-deficient gastrointestinal tumors. However, these treatments can have severe toxicity and are extremely costly, and many patients still do not respond. Additionally, once treatment begins, response evaluation may be compromised by increases in tumor size due to “flare” reactions and pseudoprogression.

In the NEWS

PET Facilities Imaging Patients for IDEAS

LisaAnn Trembath, CNMT, MSM, CRA, FSNMTS, and Adam Opanowski, CNMT, PET, NCT, RT(N)(ARRT)

Amyloid PET imaging is now a Medicare-covered benefit for patients who are enrolled in the Imaging Dementia—Evidence for Amyloid Scanning study (IDEAS). IDEAS is designed to follow 18,488 Medicare beneficiaries for four years to obtain a sufficient amount of evidence to demonstrate that knowing the results of an amyloid PET scan will help physicians make informed treatment care decisions. To be eligible for enrollment, patients must be 65 years or older and meet the Appropriate Use Criteria (AUC) developed by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer’s Association. Patient enrollment in IDEAS is initiated by study-approved and registered dementia specialists who determine eligibility and then refer potential study participants for amyloid PET imaging at a registered facility. Participating PET scan providers are reimbursed for amyloid PET scans under the CMS Coverage with Evidence Development (CED) policy that requires research study participation as a condition of Medicare payment. Sites can use any of the three FDA-approved 18F-labeled amyloid imaging agents: Amyvid™ (Eli Lilly), NeuroCost™ (Prasmal Imaging), or Vizamyl™ (GE Healthcare).

Nuclear medicine physicians or radiologists who interpret amyloid PET scans for IDEAS must complete tracerspecific reader training provided by the radiopharmaceutical manufacturer. Scanning should be performed according to the SNMMI Procedure Standard-EANM Practice Guideline for Amyloid PET. It is highly recommended that, in addition to reader training for interpreters, sites obtain training and technical support from the respective agent’s vendor to optimize image quality and standardization (also see the “TIPS for IDEAS” article in this issue). Amyloid PET images collected on enrolled IDEAS subjects will be archived and used as a resource for future research.

IDEAS is managed by the American College of Radiology. Imaging facilities interested in participating in IDEAS must have experience with brain PET (FDG or amyloid) and be accredited for neurologic PET by the Joint Commission (hospital-based sites), ACR® (American College of Radiology), IAC (InterSocietal Accreditation Commission), or RadSite™. Once a site is registered for IDEAS, it must be activated by ACR before patient enrollment can begin. Specific details about adding new site credentials to already existing accreditations are available from the individual agencies. Study information for PET facilities can be found on the study website at www.IDEAS-study.org.

References:

IDEAS Study Flow

Dementia Specialists: Screen and Consent Participants (T1) (Enrollment started Jan 2016)

Refer for Amyloid PET Scan

Amyloid PET Scan within 30 Days after T1(T2)

Treating Physician: Visit with Pt to Complete 90-day Post-Amyloid PET Assessment (T3)

Submit Pre-PET CRFs within 30 days before Amyloid PET Scan (Aims 1 & 2)

Submit PET Report, PET CRF and PET Images within 7 days after Amyloid PET Scan (Aims 1 & 2)

Submit Post-PET CRF within 15 days after T3 Visit (Aim 1)
WHAT’S HAPPENING

CTN Database and DaRT: Updates and Enhancements

John J. Sunderland, PhD, MBA

The Clinical Trials Network’s (CTN’s) online PET radiopharmaceutical production database and database reporting tool (DaRT) underwent substantial upgrades and data refresh by sites during the past year. With new features added and others expanded, including new multifield search functions, its functionality has improved considerably.

Most importantly, CTN has collected up-to-date (2016) radiopharmaceutical manufacturing information from virtually every academic cyclotron/radiopharmaceutical laboratory in the United States. Information supplied by each institution includes the radiopharmaceuticals produced, frequency of production, and regulatory status of each (i.e., IND, RDRC, etc.). The database also tracks a site’s cyclotron make and model, use of generator-produced radionuclides, and radiopharmaceutical synthesis equipment. The production capabilities of all commercial manufacturers are also included in the CTN database, and this information is currently being updated.

CTN Tests Newly Designed Phantoms

Jonathan Nye, PhD

Assessment of instrument performance and image quality are important steps when preparing an imaging site for participation in clinical trials. Establishing standardization in both the protocol performance and image creation process strengthens the quality control process, improves data quality, reduces measurement variability, and simplifies the compliance process. A critical component to achieve standardization is imaging objects of known truth that have anthropomorphic shapes mimicking real-life imaging situations.

In 2008, the SNMMI Clinical Trials Network (CTN) developed a chest patient simulator (“phantom”) to evaluate oncology PET imaging. This phantom has been successful in identifying a wide variety of scanner performance levels and stratifying these into broad classes.

The CTN database was recently introduced to a panel of pharmaceutical company and industry scientists and physicians who were given the opportunity to test the database/ DaRT’s capabilities. We are using their feedback to prepare for future enhancements and expansions, one of which is likely to include adding international PET radiopharmaceutical production laboratory information to the database.

It is envisioned that the CTN database and DaRT will be used by academic institutions, pharmaceutical companies, and biomarker developers worldwide to facilitate both regional and international collaborations and to potentially streamline logistics associated with clinical trial development using novel radiopharmaceuticals.

Tech Talk

“TIPS” TO OPTIMIZE PARTICIPATION IN THE IDEAS STUDY

Ruth Tesar, CEO, Jan Cronin, CNMT and Bruce Finley, CNMT(PET)

Northern California PET Imaging Center

The IDEAS Study currently recruiting patients (see IDEAS article in this issue), presents more moving parts than participants may have experienced using the National Oncology PET Registry (NOPR). Enrollment is more complicated, effective coordination of patients, their caregivers, referring physicians and the imaging center is essential for success. Careful review of the IDEAS website (www.IDEAS-Study.org) is necessary before and during recruitment. Timelines are critical, the billing staff, technologist workflow and involved physicians must be included in the IDEAS process. The imaging center and referring physicians at each site must be registered in IDEAS, as multiple alerts are generated that prompt specific actions for each patient. At the Northern California PET Imaging Center (NCPIC), we have identified the following key areas and “TIPS” to help avoid confusion and potential errors.

BILLING

1. Traditional Medicare (MAC) is straightforward and described well on the IDEAS website.

2. With Medicare Advantage (MA) programs, there is a learning curve on the payer side, as the MA plan is billed directly.

TIP – We developed a letter directed towards our contracted MA plans that describes the process for billing under the IDEAS CED.

TIP – Our billing staff provides patients/caregivers with their expected out-of-pocket financial responsibility for each study scan.

(The cost of radiopharmaceuticals varies)

TECHNOLOGISTS

1. Technologists must know which of the three amyloid radiopharmaceuticals is being used for a patient. Currently, NCPIC uses a particular product based on the referring physician’s choice, or our medical director chooses if the referring doctor does not.

2. Pay attention to injection techniques. Wait times between injection and scan and imaging acquisition times vary among the three agents.

TIP – We incorporated the specific scan parameters and details for each radiopharmaceutical into our scheduling software.

3. Imaging patients with cognitive impairment may be challenging.

TIP – We provide caregivers with details about the scanning process. We also prepared a video to familiarize patients with PET imaging (i.e., equipment, procedure, etc) and placed it on our website.

TIP – To avoid movement during the scan, we immobilize the head and tape a “Please Stay Still” written reminder inside the gantry where the patient can view it during the scan.

PHYSICIANS

1. The interpreting physicians must log into IDEAS to input the PET assessment after the scan is complete. They need to make this part of their routine. A new protocol for this process has been implemented in late 2016.

2. Referring physicians must complete all pre-scan paperwork before the imaging provider can start the scheduling process.

TIP – Our referring physicians’ offices provide a “heads up” about potential IDEAS patients through email notification alerts.

These tips are our best practices for our site, but you may need to create your own list based on your site’s practices and procedures. What is most important is to stay current with IDEAS by monitoring the study website and developing TIPS to better educate your staff and referring physicians.

CTN 2016 Webinar Series

The CTN 2016 Webinar Series is underway, with four more webinars to be presented live this year.

• June 23—Review of Amyloid Imaging and How to Enroll in the IDEAS Study—FREE!

• August 18—Using 68 Ga-DOTATATE in the Management of Neuroendocrine Tumor Patients—FREE!

• October 13—Using Flucluclovine in the Recurrent Prostate Cancer Patient—FREE!

• December 15—Everything You Need to Know for an IND but Are Too Afraid to Ask—FREE!

These one-hour presentations offer CE credit at a nominal fee. If you are unable to attend the live webinars, recordings are available in the SNMMI Learning Center. Check the CTN website for a full list of our offerings.
CTN Offers Services for Academic Clinical Research

The 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
- 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

DIA 2016 52nd Annual Meeting
June 26 – 30, 2016 • Philadelphia, PA

World Molecular Imaging Congress 2016
September 7 – 10, 2016 • New York, NY

2016 NANETS Symposium
September 30 – October 1, 2016 • Jackson Hole, WY

29th Annual Congress of the European Association of Nuclear Medicine
October 15 – 19, 2016 • Barcelona, Spain

The 56th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine
November 3 – 6, 2016 • Nagoya, Japan

4th Theranostics World Congress 2016
November 7 – 9, 2016 • Melbourne, Australia

RSNA 102nd Scientific Assembly and Annual Meeting
November 27 – December 2, 2016 • Chicago, IL

SNMMI 2017 Mid-Winter Meeting
January 19 – 22, 2017 • Phoenix, AZ

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