Supplement to Applied Clinical Trials

May 2008

Oncology & Clinical Trials in the 21st Century

PHOTOGRAPHY: MEDIOIMAGES/PHOTODISC, GETTY IMAGES

Stephen Pomeranz, MD, and Resham Mendi, MD

Latest Imaging Technology a Good Fit for New Therapies

Dynamic contrast-enhanced MRI meets the needs of emerging cancer therapies that suffocate tumors.

In oncology research, medical imaging is used to evaluate anatomical biomarkers such as change in tumor size. To document and quantitatively measure tumor change due to cytotoxic drug treatment, researchers measure and evaluate tumor size using computed tomography (CT) or magnetic resonance imaging (MRI) scans and Response Evaluation Criteria in Solid Tumors, known as RECIST criteria.

Emerging cancer therapies known as vascular-targeted compounds halt the flow of blood to and from the tumor, causing cell death within the tumor well before it actually begins to shrink. This cannot be measured by RECIST assessment. An emerging imaging procedure known as dynamic contrast-enhanced (DCE)-MRI is a more appropriate measurement of the effectiveness of vascular-targeted therapies

because it can show metabolic changes such as the rate of blood flow to the tumor.

This article will compare vascular-targeted and cytotoxic cancer treatments, introduce the DCE-MRI procedure, discuss the image acquisition process, and review some important considerations when planning oncology trials.

Cytotoxic vs. vascular-targeted

Cytotoxic drugs used for the treatment of cancer (chemotherapy) interrupt the division of rapidly dividing cells, resulting in the shrinkage and ultimate destruction of cancer tumors. For clinical trials focusing on the effects of cytotoxins, tumor response is used as a biomarker and is measured at various stages using X-ray, CT, and MRI and evaluated by RECIST assessment.

In contrast to cytotoxins that focus on the tumor itself, vascular-targeted treatments disrupt the tumor's blood supply. A tumor cannot survive without oxygen, which is delivered along with other critical nutrients by the blood. Disrupting the flow of blood to the tumor prevents the growth of new cells and inhibits tumor expansion.

The formation of new blood vessels by the tumor, known as angiogenesis, can be inhibited by anti-angiogenic treatments. In contrast, vascular disrupting agents target existing blood vessels. Restricting the tumor's blood flow must take into account—and possibly target—both new and established vasculature.

The potential of vascular-targeted cancer therapies is widely recognized by the medical and research communities. A variety of anti-angiogenics and vascular disrupting compounds are in development or undergoing clinical trials. Tumor size, the preferred biomarker for clinical trials involving conventional chemotherapy agents, is not appropriate for trials involving vascular-targeted treatments because shrinkage may not occur until well after blood flow has been halted. Instead, DCE-MRI is used to measure whether blood flow to the tumor has decreased, indicating the success of treatment.

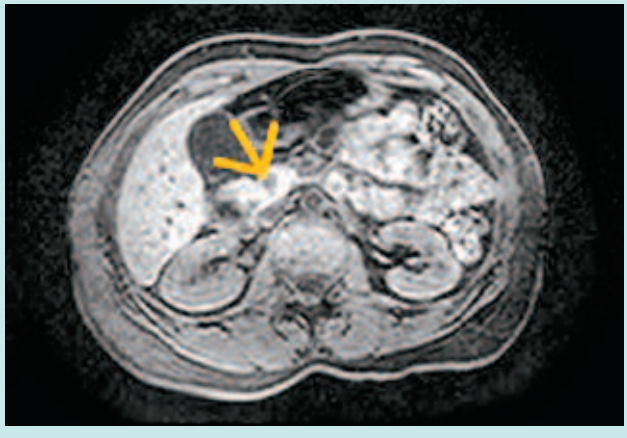
Use and benefits

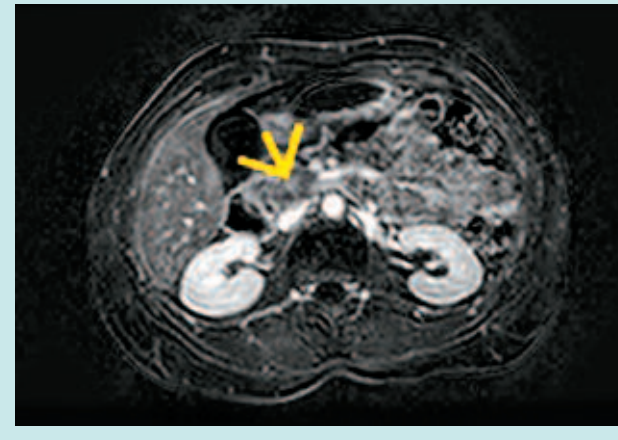
Primarily used in Phase I, the DCE-MRI provides physicians with two- or three-dimensional images taken as the patient is being administered an IV solution of paramagnetic contrast, the same gadolinium-based compound used in regular MRI studies.

Specific image acquisition and contrast injection techniques make possible the measurement of blood flow to the tumor. Prior to dynamic imaging, an initial image is acquired to establish the tumor's location and provide baseline anatomical data. Dynamic image acquisition consists of continuous scans made at five- to 10-second intervals over a five to 15 minute time frame.

Gadolinium administered concentrates at the tumor. As it circulates through the tumor vasculature, the contrast's paramagnetic properties permit blood flow to be visualized. Blood flow can be quantified using a special algorithm. Compared to tumor shrinkage, this biomarker allows the response of blood vessels to vas-

Two-Dimensional DCE-MRI Image of a Pancreatic Tumor





Figures 1 and 2. Sequential DCE-MRI imaging from the same series delineating 1 cm hypervascular enhancing lesion at the head of the pancreas (arrow) in a 44-year-old female being evaluated for mass.

Source: ProScan Imaging.

cular-targeted cancer treatments to be detected and measured very rapidly using DCE-MRI techniques.

DCE-MRI is best for studying areas of the body that are not impacted by involuntary patient movement.

DCE-MRI has many benefits in clinical trials. Besides indicating earlier anatomical response to the treatment, the technique does not involve ionizing radiation. In addition, it provides high-quality images and can be conducted using fairly common imaging center equipment, the 1.5 Tesla MRI scanner.

Planning DCE-MRI studies

Because the intricacies of DCE-MRI allow measurement variability to be introduced at numerous points, study protocol must be appropriately designed and strict quality control procedures must be followed. Due to the complexity of the imaging process, the choice of an imaging facility is critical to the success of the DCE-MRI study.

Although many imaging centers use the 1.5 Tesla MRI scanner, the image acquisition process is much more complicated than conventional MRI techniques. Imaging technologists must be specifically trained in the imaging protocols to produce high-quality images, minimize variance, and ensure accuracy. The imaging technologist must pay special attention to precontrast scanning, contrast injection rate, and dosage and image timing and analysis.

The DCE-MRI technique is most effective for studying areas of the body that are not impacted by involuntary patient movement, such as the central nervous system, pancreas, breast, brain, and bone marrow. Lung and liver tumors are more challenging because they are influenced by respiratory-related motion, leading to motion artifact. In such cases, patient movement should be incorporated into the clinical study design, including variables such as sample size, patient recruitment or exclusion criteria to filter out high-risk patients.

In addition, imaging equipment and software in multicenter trials requires standardization of equipment and uniform image acquisition across all sites. For this reason, single center trials are more feasible than multicenter trials. If a multi-center trial is needed, an imaging CRO should be selected based on its ability to manage data from multiple sites and modality vendors, and should be able to qualify hardware and software very early in the trial process.

Likewise, a standardized reading process should use independent physician readers who have received specialized training in reading and analyzing DCE-MRI images, including inter- and intravariability training prior to reading any studies. A centralized reading process ensures that the same software and analysis techniques are used by all radiologists.

Summary

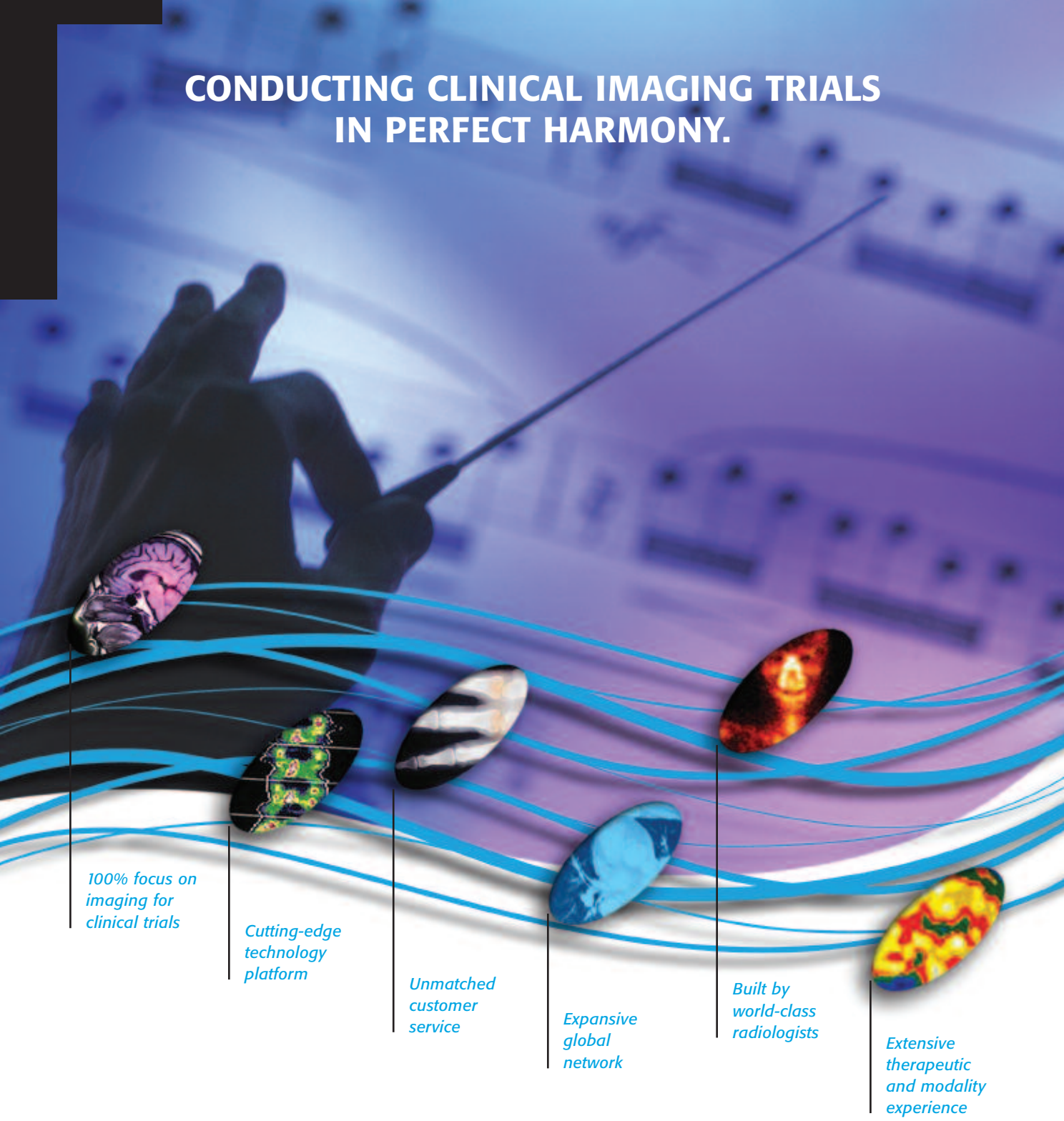
DCE-MRI is an important emerging imaging technology in the research and development of emerging vascular-targeted cancer therapies, which prevent blood flow to and from the tumor. Because it provides visualization of the tumor's vasculature, allows blood flow to be quantified and measured rapidly, and shows earlier tumor response to treatment, DCE-MRI is a more effective biomarker than tumor shrinkage for studies of anti-angiogenic and vascular disrupting compounds. Although DCE-MRI studies use standard MRI scanning equipment, the image acquisition process is much more intricate than for conventional MRI scans.

As vascular-targeted cancer therapies advance and more compounds are developed, the role of DCE-MRI technology in cancer trials will grow. Thorough study planning and protocol design, including careful training of imaging technologists and physician readers, is required to ensure high-quality images and accurate readings, as well as to minimize variance.

Dr. Stephen Pomeranz* *is the founder, chief executive officer, and medical director of ProScan Imaging, Inc., and ProScan MRI Education Foundation, and the chairman of the board at WorldCare Clinical, email: spomeranz@proscan.com.* **Dr. Resham Mendi** *is a senior radiology resident at the University of Illinois at Chicago and a former research assistant at ProScan Imaging Midtown, 5400 Kennedy Avenue, Cincinnati, OH 45213.*

**To whom all correspondence should be addressed.*

CONDUCTING CLINICAL IMAGING TRIALS IN PERFECT HARMONY.



Let WorldCare Clinical Show You How.

Experience the benefits of harmonization. At WorldCare Clinical, we provide the ability to seamlessly and effectively manage the imaging component of your clinical trial. Please call us at 1-888-816-4721 or visit www.wcclinical.com to learn more about our expertise and cutting-edge technology.

WorldCare Clinical
A ProScan Imaging Company