Although several new oncology drugs have reached the market over the past few years, more than 80% of drugs for all indications entering clinical development do not get marketing approval. There is a need for faster, more cost-effective strategies for evaluating oncology drugs and better definition of patients who will benefit from treatment. New imaging modalities including functional imaging show high promise as the basis for characterizing better biomarkers of cancer. Imaging-based biomarkers have many potential uses in all phases of the drug development process, from target discovery and validation to pivotal clinical trials for drug registration (1). Validation of imaging methods as biomarkers is complicated by the variability within and between patients, by the human observer component (which can be minimized but rarely eliminated), by the variability across imaging devices from different manufacturers, and by the need to standardize methods across institutions and centers. Some of these same sources of variability affect laboratory markers as well, but in the case of imaging it is logistically more difficult and costly to run the necessary repeatability tests on humans than it is on laboratory samples. On the other hand, the non-invasive nature of many imaging methods may be an advantage compared to biopsy for tissue genomic or proteomic data.

First, as predictive biomarkers, imaging tests can be employed to define, stratify, and enrich study groups. In vitro genomic or proteomic analysis of specimens can yield enormous amounts of molecular information from very small samples. Imaging tests provide much less molecular information. However, the information from in vitro tests usually reflects a single small locus in space and time, and many physiological parameters (such as pH or oxygenation status) may be lost in the sample preparation process. In vivo imaging methods, on the other hand, provide anatomically and/or temporally localized information, and a more accurate reflection of the true physiological state of normal or cancer cells. Capturing such spatial or physiological phenotypic information may be an important predictor for certain tumor/therapy combinations. For example, drugs such as tirapazamine (SR-4233) are most active in hypoxic tissue. PET scanning with a hypoxia marker could be a useful predictor of which patients will respond to tirapazamine. In other situations, a combination of imaging results, similar in concept to a panel of in vitro specimen biomarkers, may play a predictive role. In prostate cancer, for example, combinations of DCE-MRI, MR spectroscopy, and diffusion-weighted MR (DW-MR) are being investigated for their predictive value.

Predictive markers can also in many cases be used serially to monitor response to therapy (2). Radiologic images have been used for decades to gauge the effectiveness of various therapeutic interventions by evaluating and quantifying changes over time, such as tumor shrinkage as measured by CT or MRI. Newer imaging biomarkers are also playing a role as biomarkers for response assessment, such as FDG-PET for tumor metabolism or dynamic contrast-enhanced MR imaging to assess for vascular flow to tumors (3).
FDG-PET scans are increasingly being used to measure tumor response in a variety of drug development trials. General guidelines for measuring tumor response with FDG-PET were initially published by the EORTC PET Study Group in 1999 (4). Refinements in the recommendations for image acquisition guidelines for NCI-funded trials were published in 2006 (5).

DCE-MRI has emerged as a promising method for evaluating the effects of anti-angiogenic drugs on tumors. Remarkably, these positive results have been obtained despite considerable variation in both the methods of data acquisition and analysis. However, a fundamental issue impeding realization of this promise is that integration of results from multiple institutions and/or evaluation of the relative merits of the various methods for data analysis are difficult, if not impossible, in most cases. This is due to the variety of methods used for data acquisition and analysis and the lack of a general consensus concerning how best to acquire and/or analyze DCE-MRI data. After safety and efficacy of any new imaging method or agent have been demonstrated, the putative biomarker must be tested in therapeutic clinical trials to see if it actually performs as expected – i.e., to see if it predicts which patients will benefit from a particular therapy, or to see if biomarker changes correlate with response. The validity of such data depends on the imaging being done in standardized ways. Challenges to the development and implementation of imaging modalities in drug development include the lack of validation and standardization of new as well as established imaging methods. The identification and evaluation of biomarkers require access to and systematic analysis of large amounts of data, new technologies and extensive research resources. To this end, a variety of professional organizations are working to develop standards for hardware and software, for image acquisition protocols, and to transmit and process images in standard ways.

References


