# New Frontiers in Use of MR as a Biomarker in Therapeutics

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Abstract

Biomarkers are measureable parameters that assess the presence of disease or its response to intervention. Traditional MRI has long been used as a biomarker for many conditions. It is only recently that biomarkers have assumed more importance in the development of targeted therapeutics. Drug developers are seeking non-invasive tests that can be performed early in the course of treatment that will indicate whether a drug will have clinically relevant effects. Such "surrogate markers" are rare. To qualify as a surrogate marker, a biomarker must pass a series of milestones; several types of MRI are already advancing along this pathway(1). In this talk we use the paradigm of Dynamic Contrast Enhanced MRI (DCE-MRI) as an example of an MRI biomarker for drug development.

Drug developers are eager to develop tools that will help them identify populations that will benefit from their drug. This could make the drug development and approval process faster and less expensive. MRI is attractive because it can be performed multiple times without constraints imposed by radiation limits. In contrast, in many centers, the number of PET or SPECT scans performed per year on research protocols is restricted by the 5cGy/yr limit imposed by the Nuclear Regulatory Commission. However, MRI poses some unique problems of its own for drug developers because acquisition sequences and analysis packages vary among manufacturers and within the same manufacturer at different platform versions making it challenging to combine data from multiple institutions, a necessary condition for drug authority approval.

One goal of a biomarker for molecularly targeted therapies is determining whether the "drug hits the target". This is a necessary but not sufficient condition for success. For instance, patients with glioblastoma multiforme who receive anti-angiogenic therapy demonstrate a >90% response rate by DCE-MRI indicating that the drug is certainly hitting the target(2). However, clinical survival is improved in only a small subset of these responders re-inforcing the idea that DCE-MRI in this setting is simply a biomarker of drug activity(2). Indeed, the drug is simply reducing vascular permeability but not killing the tumor.

As with all biomarkers, MRI parameters must be above certain threshold values to be considered useful. Coefficients of variation (CoV),derived from reproducibility studies, is one way to estimate the threshold "treatment effect". In the case of DCE-MRI CoV vary from 12%-30% with required treatment effects of 24-60%. Fortunately, in the case of angiogenic inhibition, such effects are necessary for the drug to be considered effective. Standardization of analysis is a major challenge. Methods of analysis and terminology vary among experts and consensus is hard to reach. For DCE-MRI at least 4 different pharmacokinetic models are commonly reported. This makes it challenging to compare the results of one study to that of another and even more difficult to enforce uniformity among centers.

A number of trials of anti-angiogenic agents evaluated with DCE-MRI have been completed in humans. The results indicate that DCE-MRI is useful in predicting non-responders but that clinical responders are often difficult to determine on early DCE-MRI alone. Because these agents often do not have dose limiting toxicities during Phase I trials, DCE-MRI has been proposed as a method to determine dosing for Phase II studies although there is little data to support this approach. DCE-MRI with macromolecular (MM) contrast agents may be more predictive of clinical response than DCE-MRI performed with low molecular weight (LMW) Gadolinium Chelates. LMW contrast agents leak from both inflammatory and neoplastic tissue whereas MM agents are more specific for neoplastic vessels based on the larger endothelial fenestra of angiogenic vessels. Although few MM DCE-MRI studies have been performed in humans, pre clinical results are encouraging.

Thus, MRI in enjoying a renaissance as a biomarker for therapeutics. There is a growing list of MRI techniques that drug developers are using including DCE-MRI, diffusion weighted imaging and spectroscopy. MRI has natural advantages as a drug testing tool but also a number of limitations that must be overcome for this growth to continue. Looking forward into the future, the new generation of MR-based molecular imaging agents hold even greater promise as biomarkers, and perhaps surrogate markers, of therapeutic intervention.

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