How Imaging Biomarkers Can Inform Clinical Trials and Clinical Practice in the Era of Targeted Cancer Therapy

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Individualized therapy for patients with cancer, often termed personalized or precision medicine, has become an increasingly important topic with the recognition that tumors once classified solely by their tissue of origin consist of multiple genetically distinct subgroups. This ability to categorize tumors into small subgroups defined by molecular makeup can have an important impact on treatment approach because some tumors are driven by a molecular abnormality that can be targeted by specific drugs. Targeted therapies are available for tumors that express the estrogen receptor (ER) (tamoxifen, letrozole), HER2 (trastuzumab, pertuzumab), EGFR (gefitinib), the BCR-ABL fusion protein kinase (imatinib), the BRAF V600E protein kinase (vemurafenib), PD-1 ligands (pembrolizumab), and VEGF (bevacizumab), to name a few.

However, questions remain for how best to use these therapies. How can patients most likely to benefit from targeted therapy be easily and reliably identified? How should response be measured (especially because many targeted therapies are cytostatic)? Historically, these questions have been addressed by assaying tissue or serum biomarkers. However, molecular imaging offers several advantages as a cancer biomarker and is complementary to tissue sampling. Because imaging is noninvasive and nondestructive, it is capable of serial measurements of the same tissue over time, and it can be used to interrogate lesions that are difficult or impossible to safely biopsy. Imaging can also capture heterogeneity within individual lesions and across all lesions in a patient. In addition, imaging can reflect the local in vivo microenvironment of the tumor in an unperturbed state as well as in response to therapy, and in ways not adequately represented by in vitro assays.

Moving Beyond Standard Practice

Given these advantages, as well as an abundance of promising single-center data for new imaging biomarkers, one would expect to find a plethora of new imaging agents in use. Unfortunately, this is not the case, which raises the following question: Why have we not been able to move beyond standard practice, that is, 18F-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT), in the application of molecular imaging to clinical trials and clinical practice?

1. We Have Not Had the Infrastructure to Handle Novel Imaging Biomarkers in Trials

Individual institutions are capable of running pilot studies, but definitive clinical trials require the involvement of multiple institutions, creating challenges due to complexities of radiotracer supply and regulations. In the United States, investigational new drug applications sponsored by the National Cancer Institute (NCI) will make multicenter non-FDG trials more feasible and will facilitate a hybrid commercial and/or academic supply of new radiotracers. In addition, NCI support of specialized imaging clinical trials organizations, such as the American College of Radiology Imaging Network (ACRIN) Experimental Imaging Science Committee, can help provide infrastructure for molecular imaging trials. In Europe, commercial/academic collaborations are already being used; for example the recent ZEPHIR trial used 89Zr-trastuzumab PET-CT to assay the HER2 status of tumors in patients with metastatic breast cancer and to predict response to HER2-targeted therapy.

2. We Have Not Considered the Costs of These Methods the Right Way

On the surface, imaging studies add cost to clinical trials; however, they can save considerable money in the long run by (1) selecting patients likely to benefit from the drug and (2) providing a unique measure of the pharmacodynamic properties of the drug in the tumor microenvironment. These factors make it possible for imaging biomarkers to increase the probability for success in a clinical trial and to evaluate efficacy more rapidly, thereby helping to avoid investment in ineffective therapies, and promote therapies that might otherwise have been declared a failure. This strategy requires that imaging biomarkers be used in early-phase trials.

One example of the benefits of imaging is the application of 18F-fluoromisonidazole (18F-FMISO), a hypoxia-specific radiotracer, to predict the effectiveness of tirapazamine, a drug that is cytotoxic to hypoxic cells, in patients with locally advanced squamous cell carcinoma of the head and neck. In the overall study, in which imaging was not used, there was no benefit from tirapazamine, and the trial results were negative. However, 18F-FMISO PET data obtained at one of the participating centers showed that patients with 18F-FMISO uptake benefited significantly from the addition of tirapazamine to chemoradiotherapy, whereas patients without hypoxic tumors detected by PET had no benefit. Similarly, a single-center study of patients with ER-positive metastatic breast cancer receiving salvage endocrine therapy showed that 18F-fluoroestradiol (FES) PET was able to identify a subset of up to 40% of patients with absent...
ER expression who were unlikely to respond to ER-directed therapy. These examples demonstrate the use of molecular imaging for patient selection for targeted therapy. A number of other molecular imaging agents exist that can also be used to measure regional therapeutic target expression and can be used for patient selection, including HER2, the progesterone receptor, and EGFR.

Imaging can also be used to evaluate the pharmacodynamic response to a drug, providing support for a drug’s mechanism of action and likely efficacy. For example, in patients with metastatic breast cancer, 18F-FES PET-CT was used to evaluate the degree of ER blockade by tamoxifen and fulvestrant. This study demonstrated incomplete ER blockade by fulvestrant at standard dosing levels, providing a possible explanation for its lower than expected clinical performance. Although it was later determined that higher doses of the drug provided increased efficacy, time and money would have been saved if 18F-FES PET-CT had been used in early clinical trials with fulvestrant. The cellular proliferation tracer, 18F-fluorothymidine (FLT), has also been used as a pharmacodynamic marker of therapy by demonstrating a decline in cellular proliferation for both targeted and cytostatic treatments. In addition, FDG PET-CT has been used as an early measure of response to therapy in many cancers, and while successful treatment typically results in decreased FDG uptake, in some cases targeted therapy results in increased uptake. In the latter case, “metabolic flare” was best demonstrated in patients with breast cancer receiving endocrine therapy, in which a flare response was seen in 15 of 17 responders and in none of the 34 nonresponders. These examples serve as an indicator of the potential benefit, and overall cost savings, of using molecular imaging biomarkers in early drug trials. To date, however, there has been only limited support for novel imaging end points by either the pharmaceutical industry or the imaging industry.

3. Cancer Physicians May Not Be Ready to Use Biomarker Imaging to Make Treatment Decisions

We routinely rely on imaging for staging and assessment of response, but oncology does not have a tradition of using imaging to select patients for targeted treatment or to make early decisions on drug efficacy outside of clear anatomic progression. Imaging is often perceived as being qualitative and not particularly precise, subject to interpretation, and not as reliable as biopsy. Breaking tradition typically takes time; this process can be expedited with an increased emphasis on rigorous quantitative methods for biomarker imaging, and method standardization across centers. Focusing on imaging biomarkers that are related to established tissue-based biomarkers in which tissue assay is commonly used for therapeutic decision making (eg, HER2, ER, EGFR) will also help. Perhaps most important, rigorous testing of integrated imaging biomarkers in prospective clinical trials will be essential to establish the conditions for which an imaging biomarker can provide a robust and reliable measure for clinical decisions.

Conclusions

As tumors are increasingly treated based on their specific molecular profile, imaging biomarkers should become an essential diagnostic tool for selecting appropriate therapies and assessing their response to treatment. The integration of imaging biomarkers into clinical trials and clinical practice will require a concerted effort by all involved parties, including oncologists, radiologists, the pharmaceutical industry, imaging companies, and government. In the era of limited government funding, both the pharmaceutical industry and the imaging industry will need to contribute to the support of imaging biomarkers in cancer trials, realizing that in the long run their investments will pay dividends in overall cost savings and in new drugs and new imaging approaches brought to market.