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Editorial

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Imaging Biomarkers in Drug Development

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The price tag of drug development has steadily increased over the years with it now costing an average of $1.3 billion and ten years to bring a new drug to market [1]. These staggering numbers play a significant role in the rising price of drugs. For example, the anti-cancer drug, bevacizumab costs about $50,000 for one year's treatment [2]. This contributes to the unsustainable rise in healthcare expense and leads to increasing pressure to reduce the costs of drug development. Shortening the drug-development time span could be part of the solution since it is estimated that if the time span for drug development were shortened by one year, potential savings would be about $500,000. The increased use and development of novel imaging biomarkers have the potential to contribute to such time savings.

The US Food and Drug Administration (FDA) recognizes biomarkers as characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathological processes, or biological responses to a therapeutic intervention [3]. A biomarker that is intended to substitute for clinical efficacy endpoint is considered a surrogate endpoint. Currently, no imaging biomarker is accepted as an established surrogate suitable as a primary endpoint for regular FDA approval. However, if a surrogate is established as reasonably likely to predict clinical benefit superior to that of available therapies for serious or life-threatening diseases, it can be accepted for accelerated approval.

Under these criteria, biomarker imaging enabled accelerated approval by the FDA for at least 35 new oncology drugs and 47 new indications. The biomarker used in all of these trials was tumor shrinkage, as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) [4]. Other morphological biomarkers have played an important role in accelerating drug approval. For example, radiography of joint-space narrowing served to accelerate the approval of etanercept (Enbrel, Amgen) for the treatment of rheumatoid arthritis [5]. For full approval, the FDA requires that additional data be collected to demonstrate clinical benefit in the form of decreased morbidity/mortality. Of the oncology drugs mentioned above, confirmatory trials led to regulatory approval for 26 of the 47 drugs (after 7.4-12.6 yrs of drug development); confirmatory trials had not yet been completed for 14 new indications [4]. The median time between accelerated approval and regular approval of oncology products was 3.9 years (range=0.8-12.6 years) and the mean time was 4.7 years [4], representing a substantial benefit in terms of earlier availability of drugs to cancer patients. The potential for greater use of imaging biomarkers beyond physical measurements is considerable. Molecular, functional, and phamacokinetic imaging can provide important biomarker data relevant to drug development, especially for those that are directed towards a specific molecular targets that are arrived at through a greater understanding of the molecular mechanisms of disease. Biomarker imaging is especially valuable in the preclinical and early clinical phases of drug development, when it can provide data useful for internal decision making, either to drop agents that do not live up to expectations or to accelerate development of the most promising agents.

In the paradigm traditionally used in Phase I trials, the dose for further clinical development is obtained by measuring the dose limiting toxicity and maximum tolerated dose. However, for biologically targeted drugs, the effective dose may be well below the maximum tolerated dose. Moreover, the toxicity may be unrelated to the mode of action. Imaging can provide some answers. Pharmacokinetic imaging can provide important information on the distribution of the drug and determine whether the drug reaches the target, or, if excessive amounts collect in a non-target organ, estimate the potential for drug-related toxicity. Molecular and/or functional imaging can be used to demonstrate modulation of kinetic parameters and to measure the dose-relationship to determine the appropriate clinical dose.

Pharmacokinetic Imaging

Numerous studies have used radio labeled pharmaceuticals and positron emission tomography (PET) to measure the pharmacokinetics of a drug candidate. If the drug target is an infectious agent or environmental toxin, PET can be used to ensure that a sufficient concentration of the agent is circulating in the blood stream to be effective. A dynamic PET scan measures the concentration time-course in tissues of interest. Associated measurements of the blood concentration can be used to derive estimates of clearance from the blood into tissues and the ratio of concentrate on labeled drug (and metabolites) in blood and tissue. Such imaging can, for example, demonstrate that the candidate drug crosses the blood brain barrier [6].

If the target is a pathological process, imaging can be used to determine the binding efficiency and receptor occupancy [5,6]. This can be accomplished using a radio labeled agent that targets a receptor and measuring its displacement by a candidate drug. Such imaging can provide evidence that there is biological activity at doses lower than that associated with toxicity [7,8].

Alternatively, the distribution of a radio labeled drug candidate can be measured, using microdoses. In this case, the doses are so small that the FDA has waived the need to prove the safety of the imaging agent in microdosing/exploratory investigational new drug (IND) studies [9]. These studies can help to identify the best candidates for continued development and eliminate those lacking promise. Furthermore, microdosing studies can be completed faster and at less cost than traditional approaches for first-in-human studies of drug candidates.

Imaging as Prognostic Indicator

Although measurements of tumor dimensions, typically using computed tomography (CT) and RECIST, have been widely used to predict response to treatment by oncological drugs, this method has

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its limitation. The measurements are somewhat subjective and it can be many weeks before a response is observed. Moreover, it can be impossible to differentiate between tumor necrosis and viable tumor on CT using size criteria alone.

Other imaging methods may provide an answer. For example, a decrease in metabolic activity, as measured by a decrease in the uptake of 18F-fluorodeoxyglucose (FDG), visualized with PET, often precedes a tumor response as measured by RECIST. This was first demonstrated in the drug trials for imatinib mesylate (Gleevec, Novartis), a tyrosine kinase inhibitor designed to block an overactive enzyme in gastrointestinal stromal tumors (GIST). In these trials, a change in metabolic activity, measured by PET, was detected 8 days after initiation of treatment, whereas it was 2-3 months before tumor shrinkage was observed. Furthermore, the PET response correlated with a longer progression free survival at one year [10].

Since then, there has been considerable research on measuring response to therapy in solid tumors using FDG PET, which has provided evidence of the reliability of this method. As yet, there are no international guidelines or criteria for measuring tumor response with FDG PET for the purposes of drug approval [11]. However, FDG PET data are clinically used to determine response to treatment and to base changes in therapy.

Perfusion imaging may also provide useful prognostic information. Both CT and MRI can be used to estimate parameters such as blood flow, blood volume, and blood vessel permeability. In several studies perfusion imaging has demonstrated changes within a few days of initiation of treatment that may be indicative of response. For example, Willett et al. demonstrated that twelve days after a single infusion of the VEGF specific antibody bevacizumab, there was decreased tumor perfusion and vascular volume in colorectal cancer tumors and that a larger drop in blood flow was associated with better patient outcome [12].

Perfusion imaging also demonstrated normalization of tumor vessels in patients with recurrent glioblastoma in a Phase II trial, in which patients were given AZD2171, an oral tyrosine kinase inhibitor of VEGF receptors. MRI measurements showed decreased vascular permeability within one day of initiation of treatment. These findings corresponded with reduction in tumor associated vasogenic edema and clinical benefit as measured by reduced or eliminated need for corticosteroid treatments [13].

Nuclear imaging techniques may also provide early evidence of response. For example, in a clinical trial of a small molecule c-Met and VEFR inhibitor, XL184, for castrate-resistant prostate cancer, 55/65 (86%) patients showed a complete or partial resolution of bone lesions as measured by technetium 99m-methylene-diphosphonate (MDP)bone scans at six weeks after initiation of treatment. Sixty-four percent experienced decreased pain and 46% decreased or halted narcotic treatment. In contrast, there was no correlation between clinical activity and PSA levels, which has historically served as the primary endpoint in prostate cancer drug trials [14].

Other Opportunities for Biomarker Imaging

The list of other imaging methods for detecting therapeutic response is considerable. There are growing opportunities for using PET imaging utilizing novel radiotracers [8]. There are agents available that can measure DNA synthesis (a marker of cell proliferation), hypoxia, and apoptosis, all of which have the potential be used as a marker of response to cancer therapy. Amyvid, a new agent that targets beta-amyloid plaque, has recently been approved for clinical use in patients with Alzheimer's disease (AD) [14]. Although the FDA has not approved Amyvid for monitoring patient responses to AD therapy at this time, it still might be useful in early stage drug trials.

Novel modalities, such as PET/MR, which combines morphological and molecular imaging, could provide new tools for biomarker imaging. MR spectroscopy (MRS), can be used to measure several metabolites, including choline, creatine, and lactate could also provide useful early data on response to therapy. Choline phospholipid metabolism, which is associated with changes in the cell membrane, is profoundly altered in cancer and results in elevated choline peaks on MRS. Several studies have demonstrated that early changes in the choline peak are linked to subsequent tumor response in cancers such as brain, breast and prostate [15]. In some cases, unusual metabolites have been associated with disease and enzymes associated with their metabolism could be potential drug targets. For example, some gliomas are associated with high levels of 2-hydroxyketoglutarate, which is detectable by MRS [16,17].

Although the potential for increased use of biomarker imaging is clear, there is a need for caution. For example, it is possible that a biomarker is not, in fact, on the pathophysiological pathway of disease or is not on the only pathophysiological pathway. A biomarker may be unchanged if a therapy modulates the physiological pathway downstream from the site of biomarker activity or if an effective therapeutic intervention acts on a pathway that is not related to the biomarker. Moreover, differences in sensitivities between biomarker responses and clinical endpoints may also lead to biomarker failure [18]. It is, therefore, essential that there be a thorough understanding of the relationship between the biomarker, the pathophysiology of the disease, and a clinical meaningful end-point.

Despite these cautions, it is clear that there is potential for much greater use of well-selected imaging biomarkers in drug development. For example, drug developers could consider, as a matter of course, how new drugs can be labeled with positron emitters so that they can be utilized early in Phase I drug trails. In Phase II trials, including an imaging component in the trail design could provide insight into the likely effectiveness of the new treatment. The inclusion of these tools is likely to allow elimination of drugs that show little promise and the more rapid deployment of successful new drugs.

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Top

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