

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Advances and Challenges in the Use of Biomarkers in Clinical Trials

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H&O How are biomarkers used in oncology clinical trials?

BC Biomarkers are used in three ways. First, biomarkers are used for patient selection (ie, matching a patient's tumor to a specific drug), which involves testing for the presence of a mutation, amplification, or overexpression of a target. This use has been important to drugs like trastuzumab (Herceptin, Genentech). Second, biomarkers are used in phase I trials to prove that a drug engages a target and is achieving the intended pharmacologic effect. Although it is not clear that an agent successfully engaging a target necessarily leads to clinical benefit, if interruption of a given pathway is not seen, the agent is either ineffective or its effects are misunderstood. Biomarkers such as M protein in myeloma and prostate-specific antigen in prostate cancer are now accepted surrogates for clinical response in early clinical trials. In the case of myeloma, M protein was an endpoint for drug approval. Third, biomarkers can be used to help avoid or attenuate toxicity by identifying patients who are at high risk of toxicity. There has been some progress in this arena, which does not necessarily dovetail with translational research. For example, clinically beneficial pharmacogenomic tests have been developed for glucuronyltransferase, which is involved in toxicity of irinotecan, to identify patients who lack that enzyme or have a polymorphism for it that predisposes them to toxicity. This assay is not presently used widely, like similar tests used with other agents, primarily because the individual affected population is small. Most clinicians choose to forego such tests by recognizing toxicity clinically and altering the dose as appropriate, although

any patient with an asymptomatic bilirubin elevation is at risk for increased toxicity and should be tested for the UTG1A1 polymorphism.

H&O What are the current trends in the use of biomarkers in oncology clinical trials?

BC The predominant trend is clear: biomarkers are contributing to clinical trials more and more each year. In order to participate in oncology clinical trials, institutions are finding that they must have the capabilities to utilize biomarkers. The major question is whether and to what degree the use of biomarkers contributes positively to studies, and the analysis that has been completed thus far, by researchers from my institution and others, of trials from the late 1990s to the early 2000s shows that biomarkers have had some effect but not a great effect. There has been an increasing use of biomarkers, but it has been difficult to show a major impact of translational studies on drug development. The key issues in early-phase studies continue to be whether biologic activity exists and whether there is clinical response, but there is a growing awareness of the importance of showing that a drug is engaging its target and achieving biologic effects that may not be apparent in terms of tumor regression. An unpublished analysis, from my institution, of phase I trials, found that from February 2005 to the present, biomarkers have been included in most trials.

H&O What are the drawbacks to the use of biomarkers in oncology clinical trials?

BC The main drawbacks to the use of biomarkers in this setting are the high cost and the diversion of resources that may otherwise be used for other research. For instance, scientists who are interested in clinical treatment and targets become involved in this type of research, whereas they could perhaps be involved in more basic scientific research. It is not clear their involvement in this type of research will lead to more clinical benefit than if they, as in the past, concentrated on other types of science in the process of drug development. I believe it will be interesting a decade from now to discuss with those involved

whether this research was worthwhile. In my opinion, the application of biomarkers is useful and will enhance our understanding of clinical results. This research is still at an early stage, and how to use these tests and interpret their results is not fully known or proven. It is clear that certain highly beneficial drugs, such as trastuzumab, would have been impossible without the use of biomarkers. Identifying *HER2*-positive patients has been extremely important in the setting of breast cancer because of trastuzumab.

H&O How are biomarkers validated?

BC The validation of biomarkers tends to occur through clinical-trial experience. Researchers look to answer questions such as: do biomarkers help select patients? and do those patients who lack the marker not respond? One example of a biomarker that has helped researchers understand drug response is the epidermal growth factor receptor (EGFR) mutation in lung cancer. There is evidence of a high response rate in patients who have this mutation as compared to those who do not. This marker is more commonly used in the clinical-trial context than in routine patient care because clinicians often feel that they can use a patient's history (eg, nonsmoker, young, female) to discern the likelihood of the presence of the EGFR mutation. Also, because the drugs that target EGFR are relatively nontoxic, clinicians may be willing to treat such patients with EGFR inhibitors without administering a test. Therefore, the validation occurs in the context of the trial. Whether a test will be useful in clinical practice is a separate issue. Tests should be validated, but to prove that a test confers a measurable clinical benefit may be difficult.

The US Food and Drug Administration (FDA) has proposed that it should take increased responsibility for the approval of diagnostic tests, whether they are sold as a kit and used on site, which the agency already regulates, or the test is performed by a company (a "home brew"). If the FDA does begin to regulate home brew assays, it is unclear what kind of validation the agency will require. Will the FDA require that a test improve the outcome of treatment in controlled prospective trials, or only that it has an effect on treatment based on retrospective studies? At this point, the FDA's position is not fully resolved, but I believe the requirement of a demonstrable effect on survival may be too high a hurdle for the diagnostic industry. In general, the FDA is extremely supportive of any approach that helps identify and select patients for therapy to eliminate the useless administration of drugs to patients who are bound not to respond. The FDA is eager to see the field of biomarkers for patient selection continue to mature. Furthermore, the FDA is impressed with the translational work of proving that a drug hits its specified target. The

more a drug's biology and pharmacology is understood, the better its chances of approval by a regulatory agency.

H&O What does the future hold for the use of biomarkers in clinical trials?

BC There are two important aspects of the use of biomarkers that will increase in the future. First, there will be an expansion of the use of circulating tumor cells to determine whether a drug is hitting its target and whether it is achieving a biologic effect on tumor cells. A recent article by Nagrath and colleagues published in *Nature* describes a significant improvement in the assay of circulating tumor cells. Second, imaging will become increasingly important in the future, but currently positron emission tomography (PET) studies are the gold standard for revealing biologic effects that are not obvious from computed tomography or magnetic resonance imaging. A much broader variety of imaging technologies for looking at drug effects and distribution will become more widely available in the future, including PET. A wider application of PET depends on the development of sophisticated chemistry facilities on site to synthesize labeled drugs and metabolic intermediates. These technologies will certainly be applied to early-stage research. Many innovations have occurred with imaging in animals, but application of the same practices in humans has been slower. Reagents are not easily available, and where they are available, approval is needed before novel reagents can be used in humans.

H&O Could you discuss the financial burden of the use of biomarkers?

BC There is widespread interest in using biomarkers in clinical trials, but the financing for such an endeavor is not always available. Pharmaceutical manufacturers may finance the use of biomarkers, but single-institution trials and those funded by the National Cancer Institute may not have the funds required. The National Institutes of Health provides some funding for biomarker studies, but most of the current support comes from industry and from institutional budgets and philanthropy.

Suggested Readings

Chabner BA. Cytotoxic agents in the era of molecular targets and genomics. *Oncologist*. 2002;7(suppl 3):34-41.

Goulart BH, Clark JW, Pien HH, Roberts TG, Finkelstein SN, Chabner BA. Trends in the use and role of biomarkers in phase I oncology trials. *Clin Cancer Res*. 2007;13:6719-6726.

Nagrath S, Sequist LV, Maheswaran S, et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature*. 2007;450:1235-1241.