ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Advances in Biomarkers for Targeted Agents

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H&O What were some noteworthy findings presented on biomarkers at this year's American Society of Clinical Oncology (ASCO) meeting?

MM Most obvious to the attendees of the meeting was the burgeoning impact of tumor biomarkers on therapies specific for particular subtypes of tumors. Most remarkable was the presentation by Dr. Paul Chapman at the plenary session. Dr. Chapman discussed the phase III study of vemurafenib (Zelboraf, Genentech) in patients with the V600E BRAF mutation in melanoma. This study has since led to the US Food and Drug Administration (FDA) approval of vemurafenib along with the cobas 4800 BRAF Mutation Test, the diagnostic that accompanies it. Similarly, we recently saw the FDA approval of crizotinib (Xalkori, Pfizer) for non–small cell lung cancer (NSCLC) patients with the EML4-ALK translocation again identified by a particular companion diagnostic.

Another prominent presentation was Dr. Howard Scher's discussion of an effort to qualify enumeration of circulating tumor cells (CTCs) as an efficacy-response biomarker in castration-resistant prostate cancer. This research team developed a multivariate model that might be further developed as a surrogate marker for treatments that are likely to improve survival in this disease setting. The presentation highlighted the complexities that are encountered when trying to use biomarkers in such a broad-reaching and efficient way. The basic conclusion is that the goal is important and might be achieved, but it will require ongoing work with contributions both by the research team and sponsors who are conducting pivotal phase III trials in this disease/treatment setting.

These findings are exciting; however, we have not delivered them at the frequency or success rate at which the concept of targeted therapy promises, and there are many roles for biomarkers to play.

H&O Can you discuss your presentation on hypertension as a biomarker for VEGF-targeted therapy?

MM Although it is common to talk about a severe toxicity—such as hypertension—as a biomarker, one of the key points from my presentation was that instead of thinking about the categorical marker of hypertension, we really should be focusing on the quantitative marker of change in blood pressure. That being said, this issue is taking on increasing importance because the incidence of treatment-related hypertension has been associated with better outcomes in patients who received angiogenesis inhibitors, specifically inhibitors of the vascular endothelial growth factor (VEGF) signaling pathway (VSP).

Most convincing are the 2 large studies that have found an association between the development of hypertension at a landmark point, or a specific time point after initiation of treatment, and survival among patients treated with those agents. The first group to definitively nail this point down was Dr. Suzanne Dahlberg and colleagues in their *Journal of Clinical Oncology* publication in 2010 discussing bevacizumab (Avastin, Genentech) in the treatment of NSCLC, and more recently Dr. Brian Rini and associates in the *Journal of the National Cancer Institute* publication describing the association of the development of hypertension on sunitinib (Sutent, Pfizer) and overall survival in renal cell carcinoma patients.

Paying attention to quantitative changes—instead of just focusing on a categorical marker, such as achievement of blood pressure above a certain threshold—can provide important insights on the safest and most effective use of novel therapies. For example, in a 2009 publication in *Clinical Cancer Research*, we demonstrated that patients who received sorafenib (Nexavar, Bayer/Onyx) have diverse blood pressure responses to the administration of sorafenib when blood pressure is measured carefully with ambulatory blood pressure monitoring. This technology allows for collection of 40–100 blood pressure measurements over the span of a single day without causing too much disruption to a patient's life. Ambulatory monitoring gives a more precise determination of mean blood pressure than the set of office measurements we would typically perform. Continuous ambulatory blood pressure monitoring allows us to have more confidence in changes in these measurements over time compared to routine office checks, and the precision of these measurements is so useful that in the field of hypertension therapeutics, placebo trials are often not required, as there is a negligible placebo effect on ambulatory blood pressure monitoring. This allows us to detect the effects of the drug with much smaller numbers of patients. In our analysis, we found that some patients will have almost no elevation in their blood pressure after 1 week of taking a VSP inhibitor, most patients will have the typical 8–10 mm Hg diastolic elevation, and a significant subset (15–20%) of patients will have dramatic elevations in their diastolic blood pressure from 15 to 30 mm Hg in the span of 1 week.

H&O What are the implications of these findings?

MM The findings from my presentation have 2 important implications. First, a subset of patients experience severe adverse cardiac and cardiovascular events with VSP inhibitor therapy. One proposed strategy with the more potent of these drugs is to treat all patients concurrently and prophylactically with an antihypertensive drug. However, the individuals who have little blood pressure response to the VSP inhibitors would probably suffer more serious adverse events from the antihypertensive drugs than from the cancer drug. So a more personalized and effective strategy would be to evaluate blood pressure responses early in treatment and to focus blood pressure control with antihypertensive drugs on those most at risk for problems from blood pressure elevation and those who have the greatest increases in blood pressure.

The second implication was discussed by Dr. Patrick Schöffski at the ASCO meeting. Our group presented results of a dose escalation study of sorafenib in patients who were normotensive. Our primary objective was to answer the question, "Is dosing to hypertension a feasible strategy?" We found that our patients fell into 3 groups: patients who had no significant blood pressure elevation off the standard dose who developed no further elevation even after we escalated the dose, patients who had an initial elevation but had no further elevation when the dose was escalated, and patients who had a dose-response relationship. In those patients who had a dose-response relationship, only a small number actually were able to tolerate the higher dose. Thus, at least with sorafenib, the findings suggest that a dose-to-hypertension strategy would not work very well. We took away from this 2 hypotheses that warrant further investigation; one is the issue of whether—given the fact that hypertension predicted for better therapeutic outcomes in the Rini and Dahlberg studies—those individuals who are seemingly blood pressure insensitive to VEGF inhibition represent a subset of patients who will not derive any benefit from this class of drugs. The second hypothesis is that drugs that are more specific for VEGF pathway inhibition, such as the newer generation kinase inhibitors like axitinib (Pfizer) and tivozanib (Aveo Pharmaceuticals), might be amenable to blood pressure elevation-based dosing strategies.

H&O Are there downsides to using adverse events as biomarkers to determine appropriate dosing?

MM Definitely; the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) is a uniform classification system that allows a central organization to survey different drugs across different studies and treatment settings to quickly identify safety signals. This allows investigators to have some uniform way of cross comparing the severity of adverse events for one drug or one program versus another. It has never been validated as a means of stratifying patients for dosing an anti-cancer drug effectively. The downside is that dosing a patient to a particular grade toxicity is a very arbitrary plan based on familiarity with CTCAE. It does not necessarily have anything to do with how the drug works or whether it is a good strategy.

There is also an upside: for example, in the case of hypertension, investigators in the field of hypertension have spent decades understanding how to measure blood pressure accurately and efficiently, and using it as a biomarker for dosing an anticancer drug therefore comes along with a lot of conveniences and tools that may be a significant advantage over developing a biomarker for these drugs de novo.

H&O In one of your recent papers in the Journal of Clinical Oncology, you discuss tumor response. What do you think should be used instead of RECIST to determine disease progression?

MM I think the important point about this paper is made in the title, "A time to keep and a time to cast away categories of tumor response". We think that in early therapeutics development, response evaluation criteria in solid tumors (RECIST) is not a good tool pretty much for all the same reasons I mentioned for CTCAE and toxicities. It is a categorical system that is intended to make interpretation of data uniform across many sites and many centers on a reliable basis. However, it costs us significantly in power: we have a tendency to enroll many more patients to disprove a null hypothesis with RECIST, and we take away a lot less information about what a drug did or did not do in a group of patients if we focus solely on whether patients had a specific degree of shrinkage. Instead, we recommend using the increasing computing power and the analytical methods in other fields of drug development that have benefited from disease progression models, and applying them to oncology. The models are all relatively new; the first major publication discussing these models in NSCLC was by Wang and colleagues in *Clinical Pharmacology & Therapeutics*. Although it was based on the largest data set of its kind, it has not yet been externally validated in published form.

H&O What are the challenges to incorporating biomarker studies into early clinical trials?

MM It is striking how the focus of bench scientists is on innovation in discovery of biomarkers, but that the habits of clinical investigators, sponsors, and the infrastructure for clinical trials constrain innovation in the clinical development phase. For example, to make disease progression models work requires the logistical processes to allow centralized and uniform collection of imaging data. RECIST and the processes for recording RECIST responses and sharing the data with a central data monitoring committee are so ingrained and low-tech that one of the major obstacles is how to alter this process to collect and analyze a richer data set. The main advantage for using a model-based approach is that we can use already collected data to accomplish some of those goals.

The logistics of conducting clinical trials to better incorporate biomarkers for development of both the biomarkers and the drugs requires coordination, education, and agreement among investigators. This is the area in which the Biomarkers Task Force of the Investigational Drug Steering Committee of the NCI has been working for the past several years. The committee has produced guidance, published in *Clinical Cancer Research*, for investigators on uniform definitions and classification for biomarkers. It has also guided investigators on what settings and with what levels of intensity biomarkers are appropriately incorporated into early development studies. Through consensus among their many members they have provided a process that could be effectively used by investigators in both industry and academia to rapidly advance the use of biomarkers in early studies.

Suggested Readings

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507-2516.

Scher HI, Heller G, Molina A, et al. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29. Abstract LBA4517.

Maitland ML, Karrison T, Bakris GL, et al. Pharmacodynamic (PD) assessment of blood pressure (BP) in a randomized dose-ranging trial of sorafenib (S). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29. Abstract 3016.

Maitland ML, Bies RR, Barrett JS. A time to keep and a time to cast away categories of tumor response. *J Clin Oncol*. 2011;29:3109-3111.

Dancey JE, Dobbin KK, Groshen S, et al. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res*. 2010;16:1745-1755.