More Sound Cancer Therapy Biomarker Development With Active Noise Control

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Noise can be hazardous to health or simply irritating [1]. Acoustics engineers have developed methods to abate risk in hazardous environments, as well as minimize irritation and create unusual comfort in others. For example, many modern dishwashers come equipped with active noise control devices. These microphone/speaker units detect specific sound waves and generate “antiwaves” of equivalent amplitude, actively cancelling the noise [2]. This technology allows someone in your kitchen to clean dishes without having to turn up the television volume so loud as to not hear a pot of water over boiling on the stove. On international airplane flights, attendants may distribute headsets with similar devices to provide a trip free from engine noise.

Cancer therapy can be hazardous to patients, and it never seems comfortable no matter how good the supportive care. For the past decade, investigators with various skills applying numerous strategies have promised “precision” medicine. Nearly all of these efforts employ biomarkers—that is, objectively measured characteristics that are evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions [3]. However, the absence of engineering principles and methods for developing, testing, and implementing biomarkers in parallel with the development of new drugs obstructs delivery of precision medicine.

The failure to develop biomarkers soundly for drugs that disrupt the vascular endothelial growth factor (VEGF) signaling pathway (VSP) exemplifies the problem. In the past decade, nine companies have developed nine drugs that specifically inhibit the downstream signaling through VEGF/VEGF receptor-2: aflibercept, axitinib, bevacizumab, cabozantinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib. More agents in this class have been tested, but most will never become available. Each effort has been associated with numerous studies of mechanisms of action, preclinical models, and human candidate biomarkers, but there remains no qualified biomarker to improve the therapeutic index of VSP inhibitors [4–8].

In this issue, Hurwitz et al. [9] report on the candidate biomarker of change in blood pressure (BP) after beginning bevacizumab therapy. Hypertension was identified as a common occurrence and dose-limiting toxicity related to the mechanism of action of VSP inhibitors [10–13]. Measurement of BP change after starting VSP inhibitor treatment was proposed as a candidate biomarker to improve the therapeutic index of VSP inhibitors [14–16], but how to apply this marker in practice was unclear. After many preliminary reports, several well-conducted

retrospective investigations of axitinib, bevacizumab, and sunitinib suggested the early development of BP elevation after therapy to predict better treatment outcomes across multiple diseases [17–19]. In contrast, Hurwitz et al., with the largest retrospective analysis to date, only found association between BP response and tumor response in one of seven phase III trials with bevacizumab. They have clearly demonstrated that there is no basis for an oncologist using routine office BP measurements during the first eight weeks of treatment to predict whether or not a patient is benefitting from bevacizumab therapy. However, the case for BP as a biomarker for improving VSP inhibitor therapy is far from closed.

Two common and significant sources of noise that limit detection of clinically important associations in concurrent new drug and biomarker development are the (im)precision of the assay detecting the marker and the strength of the relationship between the marker and the clinical endpoint of interest. The term “noise” means that the measurements and associations have high variance. BP is a noisy biomarker. A single BP measurement in a patient reflects imprecisely the patient’s average BP. Similarly, although a patient can show early evidence of pharmacodynamic effects of docetaxel by developing neutropenia with the first dose, numerous additional variables determine whether docetaxel will in fact prolong that patient’s survival. A major challenge for the effective development of biomarkers for novel therapeutics is to identify and minimize the sources of noise. For both positive and negative biomarker studies, the reader should consider several basic questions to determine how to interpret the findings.

1. IS THIS STUDY AN EFFORT AT BIOMARKER VALIDATION OR QUALIFICATION?

Biomarker development comprises: a) method validation—proving that the assay to be used is reliable for the intended application, and b) qualification—generating evidence linking a biomarker with disease biology or drug effects, and clinical endpoints [20–22]. If the biomarker assay is not well validated, then reported associations with clinically relevant endpoints are likely to be false discoveries and require replication before progress can be made.

Hurwitz et al. reported a retrospective qualification study [9]. Given the noise of routine BP office measurements, the investigators only option to achieve the statistical power necessary to detect associations between BP and clinical endpoints was to increase the number of patients tested and the num-

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bers of sessions from which measurements were collected (here they used all sessions conducted during the first 8 weeks of therapy). To increase sensitivity for a small clinically relevant signal of association between BP changes and progression-free survival (PFS) and overall survival (OS) rates, they conducted a qualification study of the imprecise, poorly validated, non-standardized routine office BP measurement. Going back to our kitchen metaphor, this approach does not so much reduce the noise of the dishwasher as much as it increases the television volume setting.

Many clinicians tend to assume that BP measurement is routine and roughly accurate in all cases. However, the measurements as typically collected in my own clinic do not meet the minimum criteria for valid measurement in a clinical trial. Reproducible measurements require devices that have been certified according to accepted protocols [23] and used by well-trained clinicians or technicians who know how to position a patient properly and fit the properly sized cuff. Antihypertensive trials also typically take the mean of multiple measurements from one sitting. These approaches improve the precision of every data point in the clinical trial and are analogous to the active noise control employed by acoustics engineers. The enhanced precision of the assay in each patient on every occasion improves the statistical power to detect clinically important associations between the biomarker and the clinical endpoint. There might be significant impact for more precise BP measurement with validated methods applicable in the office setting.

2. IS THIS RELATIONSHIP UNIFORM ACROSS ALL PATIENTS, TUMOR TYPES, AND TREATMENTS?

BP response to small-molecule VSP inhibitors has proved to be rapid but variable. Patients who received the same dose of sorafenib and had BP measured with the most precise non-invasive method—24-hour monitoring with ambulatory devices—had very different BP responses. Some patients had no elevation at all. Most patients had the typical increase in diastolic pressure of 6–10 mmHg, whereas some patients (15%–20%) had more significant increases [15]. To evaluate the magnitude of BP increases, Hurwitz et al. [9] assessed different cutpoints. Only in the original study of irinotecan/fluorouracil/leucovorin and bevacizumab in colorectal cancer (CRC), AVF2107g [24], was there a consistent association between BP change and the clinical endpoints of PFS and OS. Intriguingly, this was detected in the patients who had diastolic BP increases >15 mmHg.

Association between BP change and clinical endpoints was not detected in patients with CRC who received oxaliplatin-based therapy or in patients with breast, renal, or pancreatic cancer. All patients had metastatic disease; however, in each

trial, bevacizumab was added to a different standard-of-care regimen. Furthermore, no association between BP response and tumor response was detected in the AVAIL trial [25], which added bevacizumab to cisplatin and gemcitabine in lung cancer patients. However, a strong association with PFS and OS was identified in the independently published analysis of E4599 lung cancer trial, in which bevacizumab was added to carboplatin and paclitaxel [17]. It remains plausible that BP is important to bevacizumab efficacy only in particular diseases when combined with specific cancer therapeutics.

3. IS THE BIOMARKER MEASURED AT THE RIGHT TIME?

For small-molecule VSP inhibitors, multiple studies identified BP changes typically within the first week, when drug concentrations reach steady state. No similar descriptive work has been published on bevacizumab. In the one positive study in this article, BP measurement was conducted more frequently (weekly) than all of the other trials. Conceivably, the longer half-life of bevacizumab means the time at which to detect optimally the interindividual differences is different from the small-molecule inhibitors.

4. WHAT ARE THE COSTS OF FURTHER DEVELOPING THE BIOMARKER FOR RELIABLE CLINICAL USE?

For many biomarkers in development, a large, negative study could serve as a clear signal to not pursue further development. Applying new biomarker technologies to inform cancer care can be an expensive and time-consuming undertaking. Even when novel biomarkers can clearly inform better care, it can be impractical to extend an exciting new discovery into routine community oncology. The time and resources committed to a development project should be proportional to the potential returns for future patients and the health care system. BP, even when time or equipment is devoted to measure with high precision, is inexpensive and already widely used in cardiovascular medicine.

This study is important for resetting expectations regarding BP as a biomarker for VSP inhibitors. Disappointingly, typical office BP measurements are not qualified as predictive markers for bevacizumab therapy. If clinicians are to deliver precision medicine more efficiently, more effort should be devoted to reducing sources of noise and employing better validated biomarkers for qualification testing in phase III trials.

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C/A: Consulting/advisory relationship; RF: Research funding; E: Employment; H: Honoraria received; OI: Ownership interests; IP: Intellectual property rights/inventor/patent holder; SAB: scientific advisory board

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EDITOR'S NOTE: See the accompanying article on pages 273-280 of this issue.