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Biomarker development in the context of urologic cancers

Gary J. Kelloff, M.D.[a], Caroline C. Sigman, Ph.D.[b,*], Howard I. Scher, M.D.[c,d]

[a] *Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Rockville, MD*
[b] *CCS Associates, Mountain View, CA*
[c] *Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*
[d] *Department of Medicine, Weill Cornell Medical College, New York, NY*

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Abstract

Background: The Food and Drug Administration (FDA) has called for the use of analytically validated biomarkers that have strong evidence of being fit for purpose to identify patients likely to respond and to evaluate the patient response to a therapy, potential toxicity, and drug resistance. This article discusses development and application of these biomarkers in the context of urologic cancers—specifically in cancers of the prostate and urinary bladder.

Methods: The FDA has defined four specific categories for contexts of biomarker use: prognostic, predictive, response-indicator, and efficacy-response (surrogate endpoints). Prognostic and predictive biomarkers include pretreatment characteristics of the patient and the tumor. Response-indicator and efficacy response biomarkers occur after treatment and show the effects of treatment on biomarkers. Efficacy response biomarkers show changes associated with clinical benefit and can be surrogates for clinical endpoints leading to drug approvals.

Results: Well-structured development plans are required to satisfy rigorous criteria that must be met to qualify biomarkers for specific contexts of use in drug development and patient management. A description of the extensive effort applied to the validation and qualification of circulating tumor cells in castration resistant prostate cancer is described as an example of the potential utility of biomarkers in urological cancers.

Conclusions: Many potential biomarkers have been identified in prostate and urinary bladder cancers, but few have sufficient demonstration of analytical and clinical validity to meet FDA standards for use in clinical settings. Circulating tumor cell (CTC) assays are particularly promising candidates for informative new biomarkers to measure disease before and after treatment. New technologies are providing opportunities for high definition, more informative analysis. Statistical and computational methodologies to describe assay results are also rapidly evolving. These advances will lead to better diagnosis, earlier indications of treatment response and failure, and better definition of patient cohorts that will respond to a specific treatment.

Keywords: Biomarker; Analytical validation; Biomarker qualification; Prostate cancer biomarkers; Bladder cancer biomarkers; Clinical utility; Circulating tumor cells (CTCs)

Introduction

Since 2000, remarkable headway has been made in our understanding of the biology that underlies development and progression of cancer [1–4]. Particularly important advances have been made in the application of genomics and proteomics to identify and characterize cancer-associated molecular and genetic alterations (e.g., microarray analysis and next-generation sequencing) and in technologies that may be used to measure these characteristics as well as to measure cellular and tissue changes (e.g., quantitative and high-definition imaging, single-cell analysis, and microfluidics). Also important is progress in the design of instruments to measure patient symptoms (e.g., Brief Bone Pain Inventory [5]) and other quality-of-life factors (e.g., patient-reported outcome questionnaires) and to provide systematic assessment of clinical observations and measurements (e.g., bone scan assay and quantitative imaging parameters). Despite these advances, many promising new drugs are failing late in development because they are tested in ill-defined patient cohorts or the gold standard end point of longer overall survival or other efficacy end points are uninterpretable because of

* Corresponding author. Tel.: +1-650-691-4400; fax: +1-650-240-4013.
E-mail address: csigman@ccsainc.com (C.C. Sigman).

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confounding factors such as additional therapies during prolonged follow-up or both. Late failures can also arise because of unexpected safety issues from long-term exposure. Drug resistance from preexisting and evolving clones, recognized clonal heterogeneity, and influence of disparate factors outside of the tumor per se are universal challenges [6,7]. All this suggests a high likelihood that the development and clinical application of effective cancer treatments need to address patient-specific, continuously changing molecular defects in the tumor itself and the tumor microenvironment. To overcome these challenges, the Food and Drug Administration (FDA) has called for the use of analytically and clinically validated biomarkers that have strong evidence of being fit for the purpose (context of use) of identifying patients likely to respond to therapy (prediction) and to evaluate patient response to therapy (response or sensitivity to the treatment), potential toxicity (safety), and understanding mechanisms associated with drug resistance either before or while on treatment [8–11]. In the following sections of this article, we discuss these specific applications of biomarkers for urologic cancers—specifically in cancers of the prostate and urinary bladder.

Types of biomarkers/uses in urologic disease

Biomarkers are characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers can be clinical parameters (such as age and performance status), laboratory measures (such as prostate-specific antigen [PSA]), imaging-based measures, or genetic and molecular determinants [12]. The FDA has defined 4 specific categories in the context of biomarker use: prognostic, predictive, response indicator, and efficacy response (surrogate end points) [9–11]. Prognostic and predictive biomarkers include pretreatment characteristics of the patient and the tumor [9,13]. *Prognostic* biomarkers are highly correlated with clinical outcomes (e.g., survival time) but may not be associated with specific mechanisms of cancer development and progression, the latter representing the drivers of tumor growth. Some of these biomarkers indicate prognosis in general—e.g., measurements of PSA [10,14]; enumeration of circulating tumor cells (CTCs) in patients with metastatic prostate cancer [10,15]; and gene expression patterns such as the OncotypeDx Genomic Prostate Score that is used as an aid to distinguish between indolent and potentially aggressive prostate cancers in men with very low-risk to low-intermediate-risk tumors based on standard clinical and pathological measures [14,16,17]. Urinary levels of the protein product of the fusion of transmembrane protease serine 2 and the v-ets erythroblastosis virus E26 homolog (avian) (ERG) genes (TMPRSS2-ERG) have been studied extensively and are used to aid in the diagnosis of prostate cancer, but have not been established as prognostic biomarkers [14,18]. Other biomarkers in bladder cancer are not as well developed as those in prostate cancer, but several indicate the likelihood of response to therapy in general, e.g., in patients with muscle-invasive bladder cancer, high meiotic recombination (MRE11) expression may be indicative of potential response to radical radiotherapy [19,20], low excision repair cross-complementation group 1 (ERCC1) expression suggests potential benefit from chemotherapy and chemoradiation [19,21–23], and low multidrug-resistance gene 1 (MDR1) expression is associated with benefit from chemotherapy [19,22,24].

Predictive biomarkers (which are often early genetic events in cancer) are used to determine sensitivity to a specific form of therapy and often reflect specific mechanisms of cancer progression, correlate with clinical outcomes (there are some exceptions to this, e.g., a cell surface protein used as the target to enhance delivery of a therapeutic is not necessarily prognostic or associated with cancer progression), and predict tumor response to specific drug interventions [9,10]. Many current drug development strategies use predictive biomarkers. For example, studies have been designed to evaluate new drugs targeting specific genes or mutations by identifying patient populations carrying these mutations (or genes) or gene expression patterns. Although not yet validated, potential predictive biomarkers in castration-resistant prostate cancer (CRPC) include changes in the androgen receptor (AR) and AR signaling axis (e.g., AR overexpression, increased androgen biosynthesis, splice variants and mutations, altered phosphatase and tensin homolog signaling, and translocations that allow the E26 transformation-specific transcription factor to be under the control of androgen) [10,14,18]. Similarly, unvalidated examples of potential predictive biomarkers in advanced bladder cancers are those measuring epidermal growth factor receptor (EGFR), HER2, and vascular endothelial growth factor receptor (VEGFR) pathways, which identify patients who are likely to respond to drugs interfering with these specific targets [19]. The aforementioned prognostic biomarkers, which are useful for managing patients with bladder cancer, are also being increasingly used in drug development trials to define patient populations, for both selecting patients who are likely to respond and excluding patients who are not [9,25]. Such biomarkers may be identified retrospectively after a trial has been completed and used as part of the eligibility criteria for future trials [9,10].

As is evident, biomarkers that predict the response of the tumor to specific drugs may also be prognostic for these patients. A biomarker that informs the choice of a specific therapy on an investigational protocol or in practice is called an integral biomarker [26]. If the biomarker is shown to be predictive, an approved companion diagnostic assay may be required before the drug can be approved for clinical use [26,27]. Under the revised FDA guidance on companion diagnostics [27], if the results of a pretreatment biomarker assay are used to guide the choice of one