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Biomarkers for immunotherapy in genitourinary malignancies

Susan F. Slovin, M.D., Ph.D.*

Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

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Abstract

Immunotherapy for genitourinary malignancies such as prostate, renal, and bladder cancers has experienced a resurgence since the development of 3 novel strategies: the autologous cellular product therapy, Sipuleucel-T for prostate cancer, the checkpoint inhibitors, anti–cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4), anti-programmed cell death ligand 1 (anti-PD1), and anti-programmed cell death ligand 1), respectively. These agents have led to strikingly durable responses in several of these solid tumors, but their efficacy has been inconsistent. Why all solid tumors are not equal in their response to these therapies is unclear. More importantly, changes in humoral or cellular responses which may reflect changes in a tumor's biology have been limited due to differences in immune monitoring and lack of consistency in established reliable immunologic endpoints. How to design immunologic end points that reflect a meaningful effect on the cancer remains a challenge for clinical trial development. The issues faced by clinical investigators and the current state of immune monitoring are discussed.

Keywords: Biomarkers; Sipuleucel-T; Ipilimumab; Nivolumab; Ki-67; MDSCs; Tregs; ELISpot; Renal cell; Prostate cancer; Bladder cancer; CTCs; PSA; PSMA; IL-2; Immunoscore; Cytokines

Introduction

Significant enthusiasm has returned for immunotherapeutic strategies that not only target a particular aspect of the immune system but can also affect the biology of the cancer and yield durable clinical responses. Immunotherapy is not new; preclinical studies have suggested that animals can be cured with a wide variety of approaches from conjugate and DNA vaccines to combinatorial schemes with chemotherapy or biological modifiers. However, stunningly successful preclinical approaches have not directly translated into success in humans. To date, although multiple clinical trials have shown benefit as manifested by improvement in both survival and clinical response, there remains a disparity between immunologic monitoring parameters, such as antibody titers or T-cell responses, and clinical benefit. Therefore, clinical trials with immunologic endpoints that may have some relevance to the biology of the cancer are needed but the assays used often lack the necessary harmonization for the evaluation of all cancers. This aspect remains an area of debate among immunology aficionados. The concept of immune biomarkers [1] has been introduced by many, with the expectation that there is an "immune signal" to indicate that the biological or tumor target has been "hit" by the immune system and has caused a change in the biology of the cancer, that is, decrease in size of a target lesion, remission, or has correlated with some immune parameter to indicate a relevant response to the therapy. The far-reaching application of this is that a particular biomarker could aid in clinical decision making in terms of which anticancer therapy to use in a particular patient or can show that activation of a particular cellular population is indicative of treatment functionality and potential response [2,3]. Many so-called biomarkers have included cell surface antigens that are overexpressed or biochemically altered from the normal conformation as the cancer undergoes malignant transformation. These include antigens that can be serologically measured such as prostate-specific antigen [4], prostatic acid phosphatase [2], or prostate-specific membrane antigen [5] or those that can be evaluated by

* Corresponding author. Tel.: +1-646-422-4470; fax: +1-212-988-0701.
E-mail address: slovins@mskcc.org

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Table 1
"Biomarkers" of disease activity

Known disease-elated biomarkers: CEA, CA-125, CA-19-9, and PSA
Blood: circulating tumor cells (CTCs)
Serum: quantitation of soluble antigen
Humoral or cellular responses, that is, T cell subpopulations
Tissue: tumor-infiltrating lymphocytes (TILs)
5T4 (Renal, breast, GI, colon, prostate, and ovarian)
Tissue expression: PSA, ACP, PSMA, PSCA, STEAP, lewisy, TF, Tn, KSA, GM2, Globo H, chromogranin, synaptophysin, and neuron-specific enolase
Molecular imaging of specific targets: AR

ACP = acid phosphatase; AR = androgen receptor; GI = gastrointestinal; PSA = prostate-specific antigen; PSCA = prostate stem cell antigen; PSMA = prostate-specific membrane antigen; STEAP = six transmembrane epithelial antigen of the prostate.

immunohistochemistry such as 6 transmembrane epithelial antigen of the prostate [6], prostate stem cell antigen [7], MUC1,2 [8], Globo H [8], GM2 [8], epidermal growth factor receptor (EGFR) [9–11], or erbB2 [9–12] receptor overexpression (Table 1). Although immunohistochemistry may be helpful in looking at overall expression markers on cancer cells, interrogation of the tumor milieu looking for relative increases or decreases in inflammatory or immune cell populations or quantitation of circulating DNA [13] and circulating tumor cell (CTC) numbers [14–17] continue to be evaluated in different clinical contexts as potential biomarkers of hitting the therapeutic target. One word of caution remains, the therapeutic target may be different from the immune target in question.

Biomarkers in cancer

There has been a major initiative in identifying an established a platform with which to implement biomarkers into large clinical trials for validation. However, it is imperative that a consistent understanding of what is defined as a biomarker, how to use it, and how to implement it into clinical trials be made before stating that any marker can be used as a biomarker. The term "biomarker" has often been used liberally to indicate that some laboratory measure is indicative in the change of the cancer. In fact, a "biomarker" is a laboratory measurement that reflects the activity of a disease process [13,18–20]. This is in contradistinction to a "surrogate marker," "a laboratory measurement used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy." Of note, governmental agencies such as the US Food and Drug Administration recognized that basing an approval on the effect of a drug on an "unvalidated" surrogate introduced additional uncertainty into the approval process.

Biomarker development has undergone a rapid acceleration, defined by 2 functional categories, prognostic and predictive. A "prognostic biomarker" may be a biological or clinical characteristic or behavior that can be measured objectively and can be correlated with an outcome for the patient. This can include patients at high risk for disease relapse and therefore may derive benefit from earlier interventions. A "predictive biomarker" offers information that may confer a likely benefit from treatment. These benefits include tumor response or improvement in overall or disease-free survival. This may be used to identify those specific patients who may derive clinical benefit from a specific treatment approach. It should be clarified that although a biomarker can be "prognostic" in predicting the probability of survival, it may also be "pharmacodynamic" to monitor treatment, may serve as a "surrogate end point to substitute for a clinical efficacy end point, and could also be "predictive" in attempting to match a beneficial drug to the patient.

One example of the need for clear definitions of these 2 biomarker paths in trying to correlate a potential predictive marker was exemplified by Stat5 status in breast cancer, which was considered as a marker for response to estrogen therapy. Prognostic factors can define the effects of patient or tumor characteristics on patient outcome, whereas predictive factors define the effect of treatment on the tumor [18]. The rationale for pursuing the role of CTCs as biomarkers emanated from analysis of 3 retrospective randomized phase III trials in colorectal cancer [14], breast cancer [15], and prostate cancer [16]. CTCs can be detected in as little as 7.5 ml of peripheral blood per PAXgene (Qiagen, Venlo, Netherlands) tube. Patients with CTCs of 5 or more have been shown to have a poorer prognosis than those who have less than 5 [17,21]. Similarly, in patients with prostate cancer, for whom the standard biomarker (prostate-specific antigen) may be unreliable or in discordance with the disease status, a more reliable assessment of biological response to treatment may be gleaned via CTC measurement, that is, a patient whose posttreatment CTC count declines and reaches zero will likely derive biological and radiographic benefit from treatment [21]. Another potentially relevant biomarker obtained from peripheral blood with relevance to prostate cancer is prostate-specific transcripts. Danila et al. [22] used a validated reverse transcriptase polymerase chain reaction assay to detect prostate-specific RNA in whole blood from 97 men with castrate metastatic prostate cancer and compared it with routine CTC collection. The gene markers included KLK3, KLK2, HOXB13, GRHL2, and FOXA1, with the plan to validate these as prognostic factors for overall survival (Danila). These genes were selected based on their overexpression in metastatic prostate cancer. A correlation was seen between detectable transcripts and CTC count. The authors concluded that the reverse transcriptase polymerase chain reaction assay was prognostic for survival. In addition, it had the discriminatory power to separate patients based on their risk phenotypes compared with standard CTC technology [22]. As in all these biomarker technologies, these observations need to be validated in