Prostate-Specific Antigen Doubling Time as a Surrogate Marker for Evaluation of Oncologic Drugs to Treat Prostate Cancer

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INTRODUCTION

With more than 230,000 new cases each year in the United States, prostate cancer is the most common cancer diagnosed among American men (1). Prostate cancer is expected to account for nearly 30,000 deaths in the United States in 2004 and consequently represents the second most common cause of cancer death in males in the United States. In addition, prostate cancer is associated with significant physical burden (including bowel, urinary, and sexual dysfunction in early-stage disease and painful bony lesions in more advanced cancers (2)). The growth and development of prostate cancer are highly variable and protracted; often, decades are required before the disease appears clinically (3). Significant evidence suggests that prostatic intraepithelial neoplasia is a precursor lesion for prostate cancer. For example, the two lesions share morphological features and genomic alterations (including architectural disorganization, enlarged nuclei and nucleoli, chromosome 8p loss of heterozygosity, and hypermethylation of GSTP1) and multifocal presentation. In addition, both lesions exhibit increased proliferation. Although the factors contributing to the development of precancerous and cancerous prostate lesions are not fully understood, candidate risk factors include age > 50 years, family history, high serum testosterone, high-fat diet, and prostatitis.

Predominantly affecting men aged 65 years and older, prostate cancer incidence rates have risen dramatically since the 1970s. Accompanying this rise has been a significant increase in the overall 5-year survival rates (75% for those diagnosed between 1974 and 1985 versus 97% for those diagnosed from 1992–1998). The increase in prostate cancer incidence may reflect the impact of widespread screening via prostate-specific antigen (PSA) testing on the detection of early-stage disease (4). Indeed, with early identification of prostate cancer with PSA, <10% of prostate cancers are now diagnosed with distant metastases, at which stage 5-year survival is only about 30%. In contrast, nearly all men with localized prostate cancer survive 5 years, suggesting that a great number of men live with prostate cancer. Nevertheless, about 2–3% of all male deaths are attributable to prostate cancer. These data indicate that the disease represents a significant public health burden and underscore the need for the development of improved diagnostic as well as treatment modalities for prostate cancer.

In addition to its significant role in the early detection of prostate cancer (5), PSA has been widely used in clinical management of the disease. PSA parameters are used, particularly in combination with other factors, to stage disease at presentation, guide selection of appropriate treatment, and predict or judge response to therapy (e.g., Refs. 6–12). However, the prognostic significance of PSA-defined recurrence—especially after definitive surgery or radiotherapy—remains unclear. Certain measures of PSA kinetics, especially a short PSA doubling time (PSA-DT) after local therapy, have been associated with an increased risk of disease recurrence and death (13–17). These findings suggest the potential uses of PSA-DT for risk-stratifying patients with rising PSA, both to select appropriate clinical management and to determine acceptability in clinical trials. For example, hormonal therapy (or clinical trials testing novel agents in addition to hormonal therapy) might be most appropriate for patients with a low PSA-DT, whereas lower-risk patients may be more suitable for testing novel therapies in a placebo-controlled clinical trial. In this article, we review the application of both static and kinetic measures of PSA in the management of clinical prostate cancer and in the testing of new therapies for the disease. We focus on the use of PSA-DT as a surrogate for prostate cancer growth and provide specific recommendations for the application of this parameter in the evaluation of oncologic drugs for prostate cancer.

KINETIC AND STATIC PSA MEASURES

Characteristics of PSA. PSA, an androgen-regulated serine protease, is a member of the tissue kallikrein family. PSA functions in part to cleave semenogelins, the predominant structural proteins in semen (18). A secretory protein produced primarily by normal prostatic epithelial cells, PSA is a major protein in the ejaculate. PSA production is maintained at diminished levels in prostate cancer cells. PSA was originally thought to be specific to the prostate, but very small amounts can be made by cells lining the urethra. PSA can also be produced by normal breast tissue, and PSA level may be a marginal prognostic factor in certain breast and gynecological cancers (19).

PSA is the most commonly used serum marker for prostate cancer. Secreted into prostatic ducts as an inactive 244-amino acid pro-enzyme (pro-PSA), PSA is activated by cleavage of seven NH2-terminal amino acids. PSA is secreted, albeit inadvertently, into the blood in an intact form, where it is rapidly bound by protease inhibitors such as α1-antichymotrypsin; how-
ever, a fraction is inactivated by proteolysis and circulates as free PSA. This proteolytic inactivation, as well as the cleavage of pro-PSA to PSA, is less efficient in prostate cancer. The ratio of free to bound PSA is reduced in the serum of patients harboring prostate cancer and has been used as an index to distinguish PSA levels caused by cancer versus those caused by benign prostatic hypertrophy (BPH). Elevated serum PSA levels occur under many pathological conditions via damage to the prostate (e.g., BPH, inflammation, and prostatitis) as well as after physical trauma to the prostate (e.g., biopsies, sex, and bicycling). PSA levels are also sensitive to the androgenic state of the patient.

PSA has had a greater impact than any other cancer-associated biomarker on the diagnosis and management of a cancer. The introduction of the serum PSA test in the late 1980s dramatically altered the presentation and management of prostate cancer worldwide. As a result, patients present at younger ages and with lower-stage disease, thereby increasing the likelihood that cancers detected on pathological examination will be organ-confined (5). This lower stage shift at diagnosis has been pronounced and indicates that prostate cancers should be diagnosed at a much earlier time, when they are curable by local therapy. Therefore, the recent trend of declining mortality of prostate cancer is attributed by many to implementation of PSA testing, but this interpretation remains controversial; critics believe the observed interval between the availability of the assay and the decline in mortality (10 years) may be too short to completely account for the decrease in deaths (20).

Use of PSA in Routine Patient Management. PSA has a role in screening, early detection, diagnosis, staging, monitoring progression, and evaluating the effects of treatment. Examples of each of these applications are detailed in the following sections. In addition, the effects of various conditions on PSA parameters are depicted in Table 1.

Serum PSA Level as a Diagnostic and Prognostic Marker. Static PSA serum levels are commonly used to screen for cancers; routinely, levels >4.0 ng/ml are considered abnormal in men aged 50–70 years, and the presence of cancer is suspected. Age-adjusted cutoff values for the normal range are <2.5, <3.5, <4.5, and <5.5 ng/ml for men aged 40–50, 51–60, 61–70, and 71–80 years, respectively (21). Lower thresholds for black versus white men have also been proposed (22). PSA cutoff values have about the same cancer detection properties as does a positive mammogram test in breast cancer in that only about 10% are positive, but biopsies are required to confirm the disease. PSA is produced by most prostate cancers, and the serum levels are a reflection of tumor volume. High PSA values are associated with advanced prostate cancer. Moderately elevated PSA is found in many organ-confined cancers, and thus the significance of PSA levels must be evaluated within the context of other disease variables. Algorithms (e.g., Partin Tables) that incorporate multiple variables (for example, presurgical PSA levels, biopsy Gleason score, and clinical stage) can accurately predict pathological findings at surgery in patients with localized prostate cancer (6, 7). In addition, such nomograms have been used successfully to predict outcome (8, 23). Recently, the addition of new markers (e.g., interleukin-6 soluble receptor and transforming growth factor β1) has shown promise for enhancing the predictive ability of nomograms in early prostate cancer (24).

Serum PSA Levels in Selecting Treatment. After prostate cancer diagnosis, the optimal treatment method is typically selected based on the Partin Tables (6, 7). In this approach, serum PSA levels have been the major contributing clinical factor in predicting the status of a patient at the time of surgery. For patients with localized, early-stage disease (stage T1–T2), the standard of care treatments include surgery (radical prostatectomy), radiotherapy (implant or external beam), and watchful waiting. Early-stage prostate cancer patients may also receive neoadjuvant (particularly in bulky disease) or adjuvant hormonal ablation therapy; recently, Casodex (bicalutamide) was shown to significantly reduce the risk of PSA progression in early-stage patients receiving either radical prostatectomy or radiotherapy as standard care (25). Adjuvant hormone ablation therapy is more frequently used for symptomatic patients with advanced-stage, locally metastatic cancer (stages T3–T4) and in metastatic cancer patients (stages N+ and M+ (26)).

Two classes of hormonal ablation therapies are most commonly used in prostate cancer. These include luteinizing hormone-releasing hormone analogs (e.g., goserelin acetate implant [Zoladex], leuprolide acetate for depot suspension [Lupron Depot], and triptorelin pamoate [Trelstar]). Equivalent to medical castration, this class of drugs prevents testosterone production by the testes. Members of a second class of drugs, nonsteroidal antiandrogens [e.g., bicalutamide (Casodex), flutamide (Eulexin), and nilutamide (Nilandron)], are commonly used in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Static and kinetic serum PSA* measures</th>
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<tr>
<td>Condition</td>
<td>Before definitive local treatment</td>
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<tr>
<td></td>
<td>Total PSA</td>
</tr>
<tr>
<td>BPH</td>
<td>++ + *b</td>
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<tr>
<td>Prostatitis</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Organ-confined cancer</td>
<td>++ +</td>
</tr>
<tr>
<td>Micrometastases</td>
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<tr>
<td>Distant metastases</td>
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* PSA, prostate-specific antigen; PSA-V, prostate-specific antigen velocity; PSA-DT, prostate-specific antigen doubling time; BPH, benign prostatic hyperplasia.

b The relative magnitude of effect of each condition on the indicated measure is expressed as (no change), +, ++, ++++, or ++++. |
combination with a luteinizing hormone-releasing hormone analog (in a combined androgen blockade). These antiandrogen drugs block the action of testosterone at the level of the prostate by competing with androgens for receptor binding. Recently, the gonadotropin-releasing hormone antagonist abarelix (Plenaxis) was shown to lower testosterone levels in men with advanced prostate cancer and was approved by the United States Food and Drug Administration for treatment of these patients (27).

Serum PSA levels fall in response to all forms of effective therapy, including radical surgery, radiotherapy, and androgen ablation. After local therapy, the major source of PSA (i.e., normal prostate) is removed or nearly completely ablated. As a result, the remaining PSA reflects primarily (if not exclusively) remaining prostate cancer. Several static PSA parameters can be used to assess the risk of progression after intervention. For example, PSA nadir after neoadjuvant therapy predicts organ confinement of the disease (12); the value after definitive local therapy is predictive of PSA failure, as well as freedom from distant metastases, time to progression to hormone-refractory disease, progression-free survival, and cause-specific survival (9–11, 28–30).

Several limitations are important to consider in the application of PSA as a marker for prostate cancer. A number of benign conditions (e.g., BPH and prostatitis), as well as physical trauma to the prostate, are associated with elevated serum PSA levels. In addition, androgen levels increase PSA production, and hormone ablation therapy reduces PSA levels. Serum PSA is low or absent in some prostate cancers; the incidence of false negative tests (i.e., patients who have prostate cancer without elevated PSA levels) ranges from 10% to 20%. Finally, PSA exists in several isoforms and proforms, and serum PSA may be either free or protein-bound.

**Kinetic Values of PSA Levels.** As prostate cancer cells accumulate, they also produce more accumulated PSA, and this is reflected by a corresponding increase in serum PSA levels (Fig. 1). This doubling time relationship of cancer cell growth and PSA levels would be most apparent in the earliest phases of growth in younger patients, when the noise in the PSA level produced by BPH is at a minimum. Serum PSA levels were assessed in a large longitudinal study of aging of normal men, some of whom subsequently developed abnormal prostate growths of BPH and cancer. Five years before cancer diagnosis, there was an exponential rise in PSA values even while in the normal range of <4.0 ng/ml (31). PSA velocity (PSA-V) levels above 0.75 ng/ml were associated with cancer and distinguished it from BPH. PSA-V was thus suggested as a potentially important early diagnostic indicator (32). In practice, PSA-V is typically calculated from at least three measurements taken over a 2-year period. Routine uses include assessment of the need for repeat biopsy in men with PSA values from 4–10 ng/ml in whom the prior biopsy was negative (33).

Because a tumor cell doubles with time and becomes exponential in growth, it is difficult to use one value for PSA-V in assessing later prostate growth. Any amount of tumor cells that double will have a measured doubling time and a corresponding PSA-DT. Typically, the correlation between the log of PSA level and time is exponential (14). PSA-DT is defined as the natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement (15). The slope of the curve obtained by linear regression of logarithmically transformed PSA data can be used if more than two PSA measures are available, or the following formula can be used if only two PSA measurements have been made:

![Fig. 1](cancancerres.aacrjournals.org) A, schematic and graphic representation of one prostate cancer cell dividing four times to produce 16 cells. B and C, continued cell division over time results in prostate-specific antigen levels doubling as cell number doubles, and the prostate-specific antigen doubling time is a constant during the log phase of growth and eventually lengthens as tumor growth slows.
PSA-DT = \[ \log (2) \times t \div \log (\text{final PSA}) - \log (\text{initial PSA}) \]

where \( t \) is the time interval from initial to final PSA determination. deKernion first applied the PSA-DT kinetics to assessing prostate cancer growth (13, 14); metastatic and local disease were associated with PSA-DT values of 4.3 versus 11.7 months, respectively. PSA-DT has subsequently been applied to predict outcomes after attempts at curative treatment, for example, after the prostate has been surgically removed or treated with ablative irradiation (15–17). Pound et al. (15) reported that a PSA-DT cutoff value of 10 months (the median in the men studied) was the most statistically significant predictor of time to distant disease progression. In the study (15), all PSA values within 2 years of PSA elevation after prostatectomy for localized prostate cancer were used to calculate PSA-DT. D’Amico et al. (17), using \( \geq 3 \) PSA measurements (each separated by \( \geq 3 \) months, and each with a PSA increase of \( >0.2 \) ng/ml), found a significant correlation of PSA-DT of \( <3 \) months with time to prostate cancer-specific or all-cause mortality. This study included men treated with surgery or radiation for localized or locally advanced prostate cancer.

In summary, PSA-V is primarily of use in measuring the early onset of prostate cancer. Once the tumor is established, PSA-DT is a measure of the tumor doubling time and thus its approximate growth rate. In contrast to PSA-V, PSA-DT is independent of the original PSA value. The absolute static level of PSA is a rough approximation of tumor volume but is confounded by the presence of BPH and variation in PSA production caused by the state of differentiation of the cancer cell and the level of androgen stimulation. Thus, PSA-DT is rapidly becoming a measurement of choice in assessing prostate cancer growth, particularly in advanced disease and in the absence of the prostate and BPH.

NEED FOR SURROGATE END POINTS IN CLINICAL TRIALS OF PROSTATE CANCER CHEMOTHERAPEUTICS

Current Opportunities. Recent breakthroughs in the understanding of the molecular basis of the development, growth, and spread of cancer have stimulated the development of numerous molecularly targeted agents that inhibit signal transduction, angiogenesis, and other pathways. Prominent examples include trastuzumab (Herceptin), a recombinant monoclonal antibody that has revolutionized treatment regimens for certain metastatic breast cancers (34–37), and the rationally designed tyrosine kinase inhibitor imatinib mesylate (Gleevec), which has transformed protocols for chronic myeloid leukemia (38, 39). These successes and the numerous drugs under development that target molecular lesions characterized in prostate cancers provide a great opportunity to continue to improve the treatment and management of this disease. For example, molecularly targeted agents being tested in prostate cancer clinical trials include the monoclonal antibody ABX-EGF, the matrix metalloproteinase inhibitor BMS-275291, bevacizumab, a monoclonal antibody to vascular endothelial growth factor, and antibodies to prostate-specific membrane antigen coupled to cytotoxic agents (40, 41). Agents that target the endothelin axis are also being investigated (42).

Evaluation of new drugs for prostate cancer has been greatly hampered by difficulties in measuring residual and recurrent disease. Occult, micrometastatic lesions may persist or develop after definitive therapy; however, these lesions may not be detectable with current imaging modalities (e.g., bone scan and computed tomography) for assessing prostate cancer progression. Indeed, the Response Evaluation Criteria in Solid Tumors criteria for assessing response and progression rely on pathological and imaging evidence of disease (43), whereas patient management of the disease is frequently driven by PSA assessments. This has significance for diagnosing early-stage disease, evaluating prognosis, and measuring response to therapy. A key goal for clinical testing of new therapies is to define the patient population most at risk for prostate cancer recurrence, morbidity, and mortality after definitive local treatment (radiotherapy or prostatectomy). Particularly challenging is the large and relatively diverse asymptomatic population of men with rising PSA after primary therapy, who lack radiographic and pathological findings of disease; a large fraction of these harbor occult metastases and may be at a 20-fold increased risk of death. Because aggressive therapy can negatively impact quality of life, it is important to target such therapy to patients with the greatest likelihood of benefit. On the other hand, patients at lower risk may constitute a more appropriate cohort for testing of novel therapies in a placebo-controlled setting. A serum biomarker such as PSA has significant potential for selecting cohorts and for optimizing both the therapeutic regimens and the design of the clinical trials in which they are tested.

Inadequacies of Current Clinical Trial Designs. End points currently used in clinical trials for prostate cancer include survival and time to progression (i.e., bone metastases as assessed by bone scan or computed tomography). However, these end points present unique difficulties because the time periods are very long, involving years. In addition, current clinical trial designs do not allow optimal dosing, scheduling, and duration of drug therapy because of the difficulty in the timely measurement of disease progression. These challenges in assessing response can lead to quality of life issues for the patient, as well as problems determining the optimal regimen and duration of therapy. In addition, it is difficult to stratify patients according to risk for disease progression and death, so that the most suitable cohort can be selected for trials studying novel interventions. In summary, the development of better and more timely measures of tumor response would not only aid cohort selection and clinical trial design and conduct but would also provide guidance for individualized therapy with approved drugs.

Defining the end point is one of the most crucial, yet most difficult, issues in trial design for prostate cancer therapy. Although survival is the ultimate end point of all clinical trials for prostate cancer, it may require a lengthy time to obtain and may be affected by interventions other than the therapy under investigation. Progression-free survival has therefore become an increasingly important end point because it may be obtained earlier and is unaffected by therapies subsequent to the trial therapy. Without clinical evidence of progression, however, the date of progression becomes difficult to determine, thus leading.
to a diverse and inconsistent set of methods to classify such patients.

In addition to using survival parameters as end points, objective measures of the response to therapy (including duration of response and duration of stable disease) may be appropriate. Because response rate varies as a function of prognostic factors as well as drug efficacy, it is important to carefully define the patient group. To maximize the benefits of therapeutic regimens being tested in future clinical trials for prostate cancer, an objective, reliable, and meaningful measure is required to assess end points.

**POTENTIAL USES OF PSA-DT IN CLINICAL TRIALS**

Both static and kinetic PSA measures have several important applications in clinical trials. As noted above, total PSA, as well as PSA nadir and kinetic variables (PSA-V and PSA-DT) have prognostic value. Thus, end points such as PSA-V, PSA-DT, and free/total PSA ratios could be considered for prevention trials in high-risk cohorts (e.g., with familial and other risk factors for prostate cancer, or prostatic intraepithelial neoplasia). The correlation of kinetic PSA measures with the risk of cancer recurrence and death after definitive local therapy suggests that these parameters could be used to select patients for intervention trials. In particular, PSA-DT can be used to identify candidates at high risk for relapse and death after radical prostatectomy or radiation therapy, for whom early treatment is likely to provide the most benefit. In addition, cohorts at low risk can be identified (for example, for placebo-controlled trials of novel therapies). Because of the link between PSA-DT and mortality, this kinetic measure can be used as a surrogate to assess outcome. These possibilities are addressed in detail below.

**Potential Use of PSA-DT to Select Cohorts for Intervention.** PSA-defined disease recurrence after definitive local therapy occurs in 30–50% of cases within 10 years of treatment; often, hormonal ablation therapy is initiated on PSA relapse. However, the relative cost/benefit ratio of this approach, especially with regard to quality of life, in this large and relatively diverse patient population is unknown. It would be preferable to target for intervention patients at highest risk for recurrent cancer and the disease-associated morbidity and mortality. This cohort is most likely to benefit from hormonal and other novel systemic therapies. Because of the increased risk and shortened time course of disease and death, a smaller sample size and shorter follow-up time would also be feasible in this cohort, facilitating the determination of efficacy of novel and standard therapies. This would especially be true if a surrogate for prostate cancer-specific mortality could be used in the study cohort.

Patients with a short posttreatment PSA-DT have almost identical estimates of prostate cancer-specific and all-cause mortality (16), and indeed PSA-DT appears to be a surrogate end point for prostate-specific mortality (17). Short posttreatment PSA-DT is also associated with a short time to disease recurrence and the associated morbidity [e.g., fractures arising from metastatic bone disease (14, 44)]. In fact, such patients may harbor occult micrometastatic prostate cancer after initial treatment. Of note, 12% and 20% of patients treated with surgery and with radiation therapy, respectively, had a PSA-DT of <3 months, suggesting a sizeable population with the observed high risk (nearly 20-fold) of short (<6 years) median survival after PSA failure (17). Thus, posttreatment PSA-DT in patients with rising PSA after local treatment identifies those at risk for recurrence, for whom early intervention may be warranted. Different trial designs may be appropriate for cohorts defined by PSA-DT value: (a) PSA-DT after local therapy of <3 months (high risk); and (b) PSA-DT after local therapy of >18 months (low risk).

Patients with a PSA-DT after local therapy of <3 months (high risk) are likely to relapse and die of prostate cancer; in the standard-of-care setting, hormone ablation therapy will be initiated on PSA relapse. Thus, the following two trial designs are possible: (a) hormonal therapy + new agent versus hormonal therapy alone; and (b) hormonal therapy followed by new agent versus hormonal therapy alone.

Patients with a PSA-DT after local therapy of >18 months (low risk) are at a substantially lower risk of disease relapse, and thus the following design is possible: treatment with new agent alone, in a placebo-controlled setting.

The strategy for patients with intermediate PSA-DT values (3–18 months) is less clear, and it is and will continue to be the subject of ongoing study.

It may also be possible to consider the application of PSA-DT to risk-stratify other patient populations. In particular, the approach may be suitable for patients failing hormone ablation. Phase III (and earlier) clinical trials are often conducted in men with hormone-refractory cancers, and thus refinement of cohort selection for such trials could have a significant impact on drug development.

**Potential Use of PSA-DT as a Surrogate of Progression-Free Survival and to Calculate Response Rate.** A posttreatment PSA-DT value of <3 months (and the specific value when ≥3 months) is a surrogate for prostate cancer-specific and all-cause mortality after surgery or radiation therapy (16, 17). In patients with rising PSA after definitive local therapy and a short PSA-DT (<3 months), it may therefore be appropriate to use the PSA-DT response (e.g., PSA failure as defined by a short PSA-DT) as a surrogate for prostate cancer-specific mortality. In particular, PSA-DT could be used as an end point in Phase II and III clinical trials testing standard hormonal therapy ± new agent (or standard hormonal therapy followed by a new agent) in the short PSA-DT cohort. PSA-DT can be also used as an end point in Phase III trials evaluating definitive local therapies.

Data also exist suggesting that PSA-DT can be a reliable end point in clinical trials conducted in patients with hormone-refractory metastatic prostate cancer. For example, in a Phase II trial of oral idarubicin, PSA was stable, and PSA-DT was lengthened in the few (3 of 26) patients who attained stable disease (45). This is a subject of high interest and is being investigated in large, ongoing studies. This cohort of patients has few treatment options, and it is important to facilitate assessment of the relative benefit of new therapies.

In all of these settings, accelerated approval could be based on the PSA-DT response, and the trial could continue to the clinical benefit end point (e.g., new radiographic findings, objective progression, and survival).
Considerations for Evaluating Newer Cytostatic Drugs. PSA-DT should be considered for use in Phase I and Phase II trials to identify the biologically optimal dose and cytostatic activity of nonconventional therapies such as signal transduction inhibitors. The duration of effect may also be an important consideration for demonstrating promise. However, it will be important to consider the mechanism of action of the drug and the likely consequent effect on PSA-DT. For example, the response to some immunological approaches may be protracted, and thus an effect on PSA may not be seen for several months. Agents that block metastasis or promote differentiation may decrease PSA-DT, but PSA levels may not be affected. A similar effect may be seen with cytostatic agents. Comparisons with pretreatment PSA kinetics may be appropriate for some classes of agents.

Trial data that demonstrate a change in PSA-DT should be used to support accelerated approval of promising new therapies. These trials would be designed to allow continuation of evaluation to radiological evidence of progression, survival, or quality of life end points or to be followed in Phase IV confirmatory trials using these standard end points.

SUMMARY AND RECOMMENDATIONS FOR USE OF PSA-DT IN EVALUATION OF ONCOLOGIC DRUGS FOR PROSTATE CANCER

Considerable data support the acceptance of PSA-DT as a marker in clinical trials for the evaluation of oncologic drugs for prostate cancer. PSA kinetic measures have numerous applications in the design of clinical trials, from prognosis to follow-up. Acceptance of PSA kinetics as a biomarker for prostate cancer will increase the number of patients eligible for clinical trials in prostate cancer. PSA-DT should be viewed as a tool that is complementary to standard criteria for disease measurement, allowing therapies to be evaluated more rapidly and unsuccessful therapies to be discontinued. These applications will benefit both the patient and the investigator. Recommendations with respect to PSA in clinical trials for prostate cancer are as follows.

(a) PSA is a reliable marker for prostate cancer progression that is validated by less controversial measures of disease progression (e.g., bone metastases).

(b) PSA measures have a role in screening, early detection, diagnosis, staging, monitoring of progression, and evaluating the effects of treatment.

(c) Whereas static PSA measures predict extent of disease, PSA-DT after definitive local treatment by surgery or with radiotherapy is correlated with survival (15–17). In addition, emerging data suggest that PSA-DT is a valuable prognostic parameter after hormonal ablation and in hormone-refractory patients.

(d) Given the significant correlation of PSA-DT with prostate cancer-specific mortality after definitive local treatment, therapeutic modulation of PSA-related parameters (especially PSA-DT) produces clinically meaningful benefits to the patient.

(e) Posttreatment PSA-DT can be used as a criterion to identify trial cohorts (e.g., at those high risk for progression, in whom hormone therapy ± a new agent can be tested).

(f) PSA-DT in the rising PSA population can also be used as a Phase III end point for studies comparing local treatments in newly diagnosed patients, if the cohort has been appropriately defined.

(g) Effect on PSA-DT can be used in go/no-go decisions in Phase II trials.

(h) Newer technologies such as proteomics and functional imaging will greatly aid cohort selection for both Phase II and pivotal trials and will eventually be valuable adjunctive end points in evaluating new prostate cancer therapies.

(i) Trial data that demonstrate significant changes in PSA-DT should be used to support accelerated approval of promising therapies. These trials would be designed to allow continuation of evaluation to improvement in disease-free survival (as assessed anatomically), survival, or quality of life end points or to be followed in Phase IV confirmatory trials using these standard end points.

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