How Much Can We Rely on the Level of Prostate-Specific Antigen as an End Point for Evaluation of Clinical Trials? A Word of Caution!

Mario A. Eisenberger, William G. Nelson*

Since its introduction for routine clinical use about one decade ago, the prostate-specific antigen (PSA) test has left a decisive imprint on prostate cancer. Perhaps the most remarkable impact of PSA testing has been the astonishing increase in the number of new cases diagnosed yearly. The American Cancer Society's estimate of prostate cancer incidence in 1996 compared with the prostate cancer incidence one decade ago has increased by more than 200,000 new cases (1). Many of these new cases are nonpalpable, radiologically unrecognizable tumors (stage T1c) diagnosed by an elevation in serum PSA levels (2,3). In addition to its use in prostate cancer diagnosis, the serum PSA test has proved to be a powerful independent prognostic factor, predicting tumor volume and stage (4). Undoubtedly, in 1996, serum PSA levels constitute a decisive factor in the selection of treatment for patients with newly diagnosed prostate cancer. Moreover, the serum PSA is widely used as a tumor marker to monitor the progress of prostate cancer treatment. This editorial will address the use of PSA testing for assessment of treatment efficacy.

In this issue of the Journal, Thalmann et al. (5) report their laboratory observations on the differential effects of suramin on the expression of PSA and on the growth of the LNCaP model of human prostate cancer. Thalmann et al. suggest that changes in PSA levels may not be an appropriate surrogate end point for antitumor response in prostate cancer patients treated with suramin because a decline in PSA level may not correlate with a decrease in tumor growth in vivo. Their findings are consistent with the initial report of La Rocca et al. (6), who found that suramin reduced PSA protein synthesis in the culture media of LNCaP cells. It is interesting that Steinkampf et al. (7) failed to demonstrate any effects of suramin on the PSA secretion into the culture media of LNCaP cells.

These interesting preclinical data should be evaluated in the context of clinical experience with suramin in patients with advanced, androgen-resistant prostate cancer, as recently reported by Sridhara et al. (8). In that study, 103 patients were treated with suramin and were followed by conventional clinical and laboratory observations, which included weekly determinations of PSA levels. The study objectives were to determine whether serum PSA changes were associated with the survival duration and to define the role of PSA levels as a surrogate end point for response to suramin treatment. The results, similar to those reported by others (9), indicated that a decline in PSA levels was a weak, but statistically significant, predictor of survival duration. Further evaluation of the data collected within the context of a landmark analysis (10), however, failed to identify a threshold value that would permit use of PSA-level decline as a response indicator. Thus, serum PSA levels, at least at this time, may not be the optimum marker of treatment response in advanced hormone-refractory prostate cancer. It is interesting that the statistical analyses by Sridhara et al. (8) also revealed that a 75% or greater decline in PSA levels was not more predictive of survival duration than was a 50% decline in PSA levels. Although this result may imply that suramin responses may not affect survival duration, this could also be explained by a possible confounding biological effect of suramin on PSA expression, not necessarily indicative of antitumor activity, as was suggested by Thalmann et al. (5).

Clearly, more clinical data are needed to further characterize the significance of PSA changes with regard to the therapeutic benefits of suramin on prostate cancer. To this end, suramin is being tested in a prospectively randomized, placebo-controlled, multi-institutional study sponsored by Parke-Davis, Ann Arbor, MI, in which quality of life, time to disease progression, survival duration, and serial changes in PSA levels are being evaluated simultaneously.

The implications of the study by Thalmann et al. (5) may actually be even broader than asserted by the authors, since similar effects on PSA expression have been reported with other drugs, including agents commonly used to treat prostate cancer, such

*Affiliations of authors: Department of Oncology and Department of Urology, The Johns Hopkins University, Baltimore, MD.

Correspondence to: Mario A. Eisenberger, M.D., The Johns Hopkins Oncology Center, 600 N. Wolfe St., Rm. 173, Baltimore, MD 21287.
as doxorubicin and vinblastine (11), and new compounds, such as the antimetastatic agent carboxyamidotriazole (12). An up-regulation (i.e., increase) in PSA expression has been reported to accompany treatment with agents such as phenylbutyrate and phenylacetate, drugs in active development for use against prostate cancer (13).

The possibility that a drug might affect PSA expression adds another level of complexity to the controversies concerning the use of PSA levels as a surrogate end point for clinical trials. If, as in the study by Thalmann et al., preclinical studies can reliably anticipate effects of chemotherapeutic agents with the cellular mechanisms on PSA expression, then clinical trials might be designed with such effects in mind. Such an approach is currently being explored at the Clinical Pharmacology Branch of the Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, where candidate drugs for prostate cancer are increasingly being evaluated for effects on PSA messenger RNA expression and PSA production and secretion (Figg W: personal communication).

As we gain a better understanding of the biology of prostate cancer, specific knowledge about the various biological properties of new anticancer drugs will prove critical for rational drug development for this disease. Fig. 1 illustrates different classes of agents, separated by their mechanisms of action and their possible effects on clinical and laboratory treatment end points. Fig. 1 demonstrates the extraordinary level of complexity facing clinicians involved in testing of new therapies in prostate cancer and suggests that clinical trial end points may need to be selected depending on the class of agent under study.

Finally, routine use of serum PSA determinations to monitor the progress of prostate cancer and to drive treatment decisions has induced an advanced prostate cancer “stage migration.” The category of patients with classical stage D2 prostate cancer is being replaced by that of patients with “a rising PSA” as the only manifestation of disease activity (Fig. 2). In fact, accrual of patients with stage D2 disease to clinical trials in cooperative groups has dramatically declined over the past few years. While the natural history of the “rising PSA patient” needs to be more precisely defined, clearly, such patients will continue to constitute a significant proportion of the patients referred for clinical trials in prostate cancer. The study by Thalmann et al. (5) reported in this issue of the Journal underscores the importance of understanding the significance of PSA changes in the context of new drug development in this group of patients.

References

(3) Stormont TJ, Farrow GM, Myers RP, Blute ML, Zincke H, Wilson TM, et al. Clinical stage B0 or T1c prostate cancer: nonpalpable disease identified...
Treasure Hunt for Human Papillomaviruses in Nonmelanoma Skin Cancers

Robert D. Burk, Anna S. Kadish*

The article by Shamanin et al. (1) in this issue of the Journal reports the detection of a wide spectrum of human papillomaviruses (HPVs) in nonmelanoma skin cancers from both immunosuppressed and nonimmunosuppressed subjects. The high prevalence of HPV DNA detected in squamous cell carcinomas (65%) and basal cell carcinomas (60%) of immunosuppressed patients and the moderate prevalence in lesions from immunosuppressed patients (31% and 36%, respectively) suggest a potential role for HPV infection in the etiology of these lesions. Although Shamanin et al. do not address the role of these HPVs in the lesions in either epidemiologic or molecular terms, they do set the stage for the next phase of investigations.

The take-home message from the study by Shamanin et al. (1) and from a recent study by ter Schegget's group (2) is that a wide diversity of HPV types can be detected in cutaneous neoplastic lesions of the skin, particularly those from immunosuppressed individuals. The one important caveat in these studies is that HPV detection by enhanced polymerase chain reaction (PCR) detection methods is not necessarily equivalent to infection with HPV. Shamanin et al. have developed a very complex method for the molecular amplification and characterization of HPVs in the skin lesions. Even when one is familiar with HPV PCR methodology, it is hard to follow the complicated strategy employed in which multiple primer pairs, reamplification, and nested PCR were used (1,3). The authors, however, provide convincing data that they, in fact, have detected a large group of new HPV DNA types. This proof is in the sequences.

HPVs are typed or classified according to their genome sequence, since standard methods used in virology (i.e., culture and/or serology) have not proved efficacious for HPVs (4). The identification of a broad spectrum of HPVs is dependent on the PCR primer system used. Thus, using a comprehensive PCR system (1,3), Shamanin et al. purposely searched for a group of new viruses. The final detection of an HPV was based on the sequence of the PCR product. This is clearly a strength of the study. The challenge for molecular virologists, however, will be to develop a simpler PCR strategy for the detection of cutaneous HPVs. Development of such a strategy will now be facilitated by a growing database of cutaneous HPV sequences, which should allow the design of consensus primers for PCR. For example, the availability of consensus primers that amplify a broad spectrum of HPV types in the genital tract has been instrumental in revolutionizing the molecular epidemiology of cervical HPV infection and solidifying the role that these viruses play in cervical cancer [for review, see (5-7)]. Prior to use in epidemiologic studies, however, the PCR system will need to be validated (8).

Many of the skin lesions described by Shamanin et al. (1), such as keratoacanthomas, resemble warty, hyperplastic lesions, and pathologists reviewing such cases frequently observe cytologic changes resembling the cytopathic effects of HPV (koilocytosis-like). Many squamous intraepithelial lesions in the skin and in other sites, such as the laryngeal mucosa, resemble those described in the genital tract. Basal cell carcinoma is generally distinctly different from squamous cell carcinoma;

*Affiliations of authors: R. D. Burk (Departments of Pediatrics and Microbiology and Immunology), A. S. Kadish (Department of Pathology), Albert Einstein College of Medicine, Bronx, NY.

Correspondence to: Robert D. Burk, M.D., Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461.