Introduction

Prostate cancer is the most commonly diagnosed cancer among American men and the second leading cause of cancer deaths in that group. An estimated 179,500 new cases were diagnosed in 1999, and 37,000 men were expected to die from the disease [1]. Although radical prostatectomy and external beam radiation therapy have curative potential in localized disease, metastatic prostate cancer is currently treated only palliatively. Initial treatment of symptomatic metastatic disease consists of androgen ablation through either medical or surgical castration. Often, an antiandrogen is added to achieve complete androgen blockade, although the necessity for this maneuver is still controversial [2]. This initial hormonal maneuver successfully decreases or stabilizes both cancer symptoms and prostate-specific antigen (PSA) in approximately 80% of patients. Response to hormonal manipulation, however, is limited. Studies examining the average duration of response to orchiectomy, medical castration monotherapy, and complete androgen blockade demonstrate variable results; overall, the mean duration of response is 18 to 24 months. Almost invariably, the cancer cell phenotype undergoes a significant and irreversible change, which makes it unresponsive to hormonal manipulation. The exact mechanism of this alteration is unclear, although both genetic and epigenetic events most likely play a role [3,4•]. Androgen independence may be due to the existence of a small subset of hormone-insensitive cells within the original tumor, which gradually gains a selective advantage as the majority of hormone-dependent and hormone-sensitive cells succumb to hormone ablation. Alternatively, the development of androgen independence may be due to mutations or alterations in the androgen requirements of the prostate cancer cell line. Unfortunately, without further treatment, more than half of these newly hormone-refractory patients will die within 1 year of disease progression.

Prostate-Specific Antigen and Other Markers of Response

Prostate-specific antigen is a 34-kD glycoprotein found almost exclusively in normal and neoplastic prostate cells. It has been validated as a prognostic marker for patients with apparently localized disease, as a marker of treatment failure after localized radiation or prostatectomy [5,6], as an indicator of response to androgen blockade therapy [7,8], and as an indicator of tumor progression in advanced hormone-refractory prostate cancer [9]. Many patients with metastatic disease will have changes in PSA level that precede changes in their bone scans; thus, the validity of biochemical response as an indicator of progression and response to therapy is a crucial issue. The degree to which PSA changes correlate with response to antitumor treatments is of major significance in the treatment of advanced hormone-refractory disease because only about 20% of patients have bidimensionally measurable disease [10].

Recently, several important studies have validated prostate-specific antigen (PSA) as a reliable measure of response to chemotherapeutic treatment in advanced hormone-refractory prostate cancer. Furthermore, although chemotherapy in this setting has always been considered palliative, several analyses of recent clinical trials have demonstrated a significant association between declines in PSA values of 50% or more and prolonged survival. Mitoxantrone, in combination with prednisone, has been shown to provide significant palliation and improved quality of life. The use of combinations of chemotherapeutic agents also seems to provide significantly superior objective and subjective responses compared with single-agent regimens. In particular, estramustine has been shown to synergize many of the agents used in prostate cancer treatment and has been demonstrated to provide significant palliation and decline in PSA levels in combination with vinblastine, vincristine, etoposide, paclitaxel, and docetaxel. The results of several important trials of the taxanes both as single agents and in combination with estramustine have been completed in the past year and have demonstrated that these agents are very effective in the treatment of hormone-refractory prostate cancer.
There seems to be no significant association between baseline serum PSA concentrations and outcome in advanced hormone-refractory prostate cancer, nor is there a correlation between PSA concentration and disease volume in this population. Although the role of PSA as a marker of response in hormone-refractory prostate cancer is still somewhat controversial, a number of investigators have recently reported an association between survival and PSA response to treatment with chemotherapy. Several recent articles have examined the correlation between PSA declines and survival as well as numerous other potential markers of progression and response in advanced prostate cancer [11,12••,13]. Whereas certain kinds of anticancer therapies, such as differentiating agents and suramin, elicit unique PSA responses owing to the nature of those agents, generally decreases in PSA in response to chemotherapy are an indication of positive response. Post-therapy declines in PSA concentration of 50% or more at 4, 8, and 12 weeks have been shown to be associated with significant increases in survival in patients treated with traditional cytotoxic chemotherapeutic agents [14].

A landmark study of more than 100 patients with hormone-refractory prostate cancer treated in two consecutive trials at the University of Michigan (Ann Arbor, MI) and Wayne State University (Detroit, MI) evaluated PSA response as a predictor of survival [15•]. All patients were treated with a combination of estramustine and etoposide. The data demonstrated a statistically significant increased survival rate in patients with a 50% or greater decrease in PSA 8 weeks after the initiation of therapy. Median survival from the 8-week landmark was 91 weeks in patients with a 50% or greater decline in PSA concentration versus 38 weeks in patients without a decrease of that magnitude. The study furthermore demonstrated that a decrease in PSA level of 50% or greater was also associated with a response in soft tissue lesions.

Scher et al. [16••] at Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) also evaluated PSA as an outcome measure in a number of phase II trials at their institution. This analysis of 254 patients with androgen independent, metastatic prostate cancer evaluated a large number of potential predictors of survival: post-therapy PSA response, baseline hemoglobin levels, serum lactate dehydrogenase (LDH) level, serum acid phosphatase levels, serum alkaline phosphatase levels, serum creatinine levels, serum albumin levels, serum glutamic-oxaloacetic transaminase levels, serum testosterone levels, age, performance status, pretreatment PSA value, and histologic grade of the tumor at the time of diagnosis. Multivariate analysis showed that a post-therapy decline of 50% or more at both 8 weeks and 12 weeks was a statistically significant predictor of improved survival. Median survival in the group of patients with a 50% or greater decrease in PSA 8 weeks from baseline was 23.6 months, versus 12.3 months for those who did not respond with a decrease of this magnitude. Similarly, using a 12-week landmark, median survival was 25.3 months for responders and 13 months for nonresponders. Additionally, the multivariate analysis demonstrated that elevated serum LDH level, decreased baseline hemoglobin level, and younger age (<70) all had a statistically significant negative effect on outcome.

The investigators then used a combined independent dataset of 541 patients from two randomized phase III trials to validate their results. The four major predictors from the MSKCC study (50% or greater decline in PSA level at 12 weeks, baseline LDH and hemoglobin levels, and age) were then used to calculate a risk score for each patient in the independent data set using the following model:

$$R_j = 0.834864 \times 50\% \text{ PSA decline within 12 weeks} + 0.002504 \times \text{baseline LDH} - 0.193959 \times \text{baseline hemoglobin} - 0.022341 \times \text{age}$$

Patients were then assigned a risk score and grouped into low-, intermediate-, and high-risk groups. Median survival of the three groups was 23, 17, and 9 months, respectively. Predicted survival for the three risk groups classified by this described model were then plotted against the observed Kaplan-Meier curve for each risk group. Predicted and observed survival rates were similar at 1 and 2 years; a slight discrepancy in the year 3 data may, investigators believe, reflect the small population of survivors at that mark. Interestingly enough, performance status, which has often been validated as a predictor of response, did not demonstrate statistically significant predictive value. As the study authors acknowledge, however, the MSKCC cohort had a very high median performance status, which may have had an effect on the analysis. In addition, the number of responders with a significant posttherapy decline in PSA value was relatively low (10% with a decline of 50% or more at 8 weeks and 12% at 12 weeks in the MSKCC group; 10% and 13%, respectively, in the independent dataset). The response range (10%–12%) may be due to the agents used in those trials. The MSKCC trials used a variety of nontoxic agents, including suramin (39.4%), rhenium-186 hydroxyethylidene diphosphonate (28%), triple-dose bicalutamide (16.1%), 13-cis-retinoic acid and interferon alfa (6.3%), edatrexate (5.5%), and all-trans-retinoic acid (4.7%). The independent dataset group was treated mainly with second-line hormonal manipulations: larnizole, prednisone, and cyproterone acetate. This may also have had an impact on the analysis. Most of the studies showing a survival advantage to a greater than 50% PSA decline have used traditional chemotherapeutic agents and responses have been in the range of 40% to 65%.

Another very important study examined the dynamic response of PSA over time through measurements of PSA velocity [17]. Because, according to the authors of this study, both PSA and the probability of death are “moving targets,” tracking response markers over time may provide a more accurate prediction of survival. This analysis focused on a group of 148 men treated in a cancer and leukemia group B (CALGB) phase II trial comparing low-dose megestrol acetate (160 mg/d) with high-dose megestrol...