PROGNOSTIC INDICATORS IN HORMONE REFRACTORY PROSTATE CANCER

Daniel J. George, MD, and Philip W. Kantoff, MD

Because the natural history of prostate cancer is highly variable, prognostic indicators that can predict survival and the response to treatment are needed to help clinicians appropriately manage the care of patients. Additionally, prognostic factors can offer insight into tumor biology and, ultimately, may suggest targets for the development of novel therapeutics. For patients with newly diagnosed prostate cancer, several prognostic indicators, including serum prostate-specific antigen (PSA) values, pathologic grade, and clinical stage, have helped define the likelihood of organ-confined disease and disease-free survival rates with local therapy. Nonetheless, the desire to develop better indicators has driven the application of new technologies for this clinical scenario.

In patients with metastatic prostate cancer, factors that can predict the length of response to androgen-ablative therapy have been sought. In the vast majority of these patients, tumors initially regress with androgen-independent tumor growth and so-called “hormone refractory prostate cancer.” Conceivably, one could imagine that if good-risk individuals (i.e., patients with a predicted prolonged response to androgen-ablative therapy could be identified a priori, they may benefit from modified strategies such as intermittent therapy or peripheral androgen blockade. Conversely, poor-risk patients (i.e., those destined to relapse quickly from androgen deprivation) may benefit from more aggressive multimodality approaches, such as those currently being tested.

For physicians managing patients with hormone-refractory prostate cancer, prognostic indicators could potentially be useful. By better understanding the prognosis for such patients, clinicians might help them prepare and cope with their disease. Such factors could also indicate which patients are more likely to benefit from treatment. Researchers might use functionally significant molecular markers associated with a poor prognosis to identify patients for whom specific new agents are appropriate. For several reasons, prognostic factors have not yet served these purposes.

During the past 40 years, many studies have evaluated the prognostic significance of certain parameters in hormone-refractory prostate cancer. Table 1 lists some of the more
Table 1. ANALYSES OF PROGNOSTIC FACTORS IN HORMONE REFRACTORY PROSTATE CANCER

<table>
<thead>
<tr>
<th>Published Studies</th>
<th>Significant Factors by Univariate Analysis ( (P &lt; 0.05) )</th>
<th>Factors Evaluated by Univariate Analysis ( (P &gt; 0.05) )</th>
<th>Significant Factors by Multivariate Analysis ( (P &lt; 0.05) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry, et al (^{11})</td>
<td>PS, alb, age, hgb, ACP, AP, SCOT, LDH, pain, mets</td>
<td>Race, prior XRT, s/p orch, CEA</td>
<td>ND</td>
</tr>
<tr>
<td>DeWys, et al (^{12})</td>
<td>PS, weight loss, protein aversion, appetite, bone or liver metastases</td>
<td>Age, initial ACP, prior XRT, measurable disease</td>
<td>PS, bone metastasis, weight loss, protein aversion</td>
</tr>
<tr>
<td>Emrich, et al (^{13})</td>
<td>PS, pain, hgb, anorexia, weight loss, ACP, AP, bone metastasis</td>
<td>Tumor grade, age obstructive symptoms</td>
<td>Anorexia, ACP, pain, AP, PS, hgb, age</td>
</tr>
<tr>
<td>Manni, et al (^{14})</td>
<td>PS, hgb</td>
<td>Site of metastasis, age, time to relapse after castration</td>
<td>PS, time to relapse after castration, hgb</td>
</tr>
<tr>
<td>Fossa, et al (^{15})</td>
<td>Hgb, fatigue, quality of life</td>
<td>PS, age, time of diagnosis, PSA ACP, bone scan, AP, pain</td>
<td>Hgb, PSA, fatigue</td>
</tr>
<tr>
<td>Petrylak, et al (^{16})</td>
<td>LDH, AP, SCOT, liver metastasis, PS, prior XRT</td>
<td>Age, pain, ACP, hgb, prior chemotherapy, bone metastasis, s/p orch</td>
<td>Log of LDH and AP</td>
</tr>
<tr>
<td>Kelly, et al (^{17})</td>
<td>PS, ACP, SCOT, hgb, LDH, &gt;50% PSA decline</td>
<td>Age, bone scan, initial PSA, ACP, creatinine, site of metastasis</td>
<td>&gt;50% PSA decline ln of LDH</td>
</tr>
<tr>
<td>Stridhara, et al (^{18})</td>
<td>Hgb, LDH, alb, baseline PSA</td>
<td>PS, ACP, AP, age, creatinine</td>
<td></td>
</tr>
<tr>
<td>Pienta, et al (^{19})</td>
<td>PS, baseline PSA, &gt;50% or &gt;75% PSA decline at 8 weeks</td>
<td>LDH, hgb, PSA, AP</td>
<td>Hgb, LDH, alb, PS, baseline PSA, percent change in PSA</td>
</tr>
<tr>
<td>Smith, et al (^{20})</td>
<td>PS, baseline PSA, &gt;50% or &gt;75% PSA decline at 8 weeks</td>
<td>AP, hgb, PSA decline at 4 weeks, measurable disease, age, LDH, prior XRT/chemotherapy</td>
<td>PS</td>
</tr>
</tbody>
</table>

| PS | = | performance status; ACP | = | prostatic acid phosphatase; AP | = | alkaline phosphatase; XRT | = | radiotherapy; s/p orch | = | orchietomy; CEA | = | carcinoembryonic antigen; ND | = | not done; LDH | = | lactate dehydrogenase. |

notable reports over the past 20 years and the factors that have been evaluated. Unfortunately, most of these studies have been retrospective and nonrandomized. Prospective randomized studies are needed to validate the importance of potential prognostic factors. The disease parameters studied thus far have been largely descriptive of either the patient and his overall condition (i.e., performance status, weight loss) or of the cancer and the extent of disease. Factors that pertain to a certain biologic behavior or degree of aggressiveness (e.g., the presence of hepatic metastases, cancer-related pain, or the rate of rise of serum PSA levels) have been evaluated to some extent, but because of the difficulty of obtaining tumor tissue in these patients, evaluations of molecular markers and specific targets for therapy have been hindered. Although modest progress has been made in the palliation of hormone-refractory prostate cancer, treatments with proven impact on overall survival are lacking. This review summarizes the current data on prognostic indicators in hormone-refractory prostate cancer, their limitations, and areas of future development.

PERFORMANCE STATUS

More so than any other single factor, investigators have used performance status to predict survival in patients with hormone-refractory prostate cancer. Despite the inherent subjectivity in rating the “performance” of a patient, including the various scales used (e.g., Karnofsky (KPS), Zubrod), and despite interphysician variability, performance status is a reproducibly important prognostic factor. In early studies, survival differences were noted in patients with severely limited activity levels (partially or totally bedridden status). Most subsequent studies have de-
ected a significant difference in prognosis based on the patient’s ambulatory status (performance status <2 or KPS ≥ 80% versus performance status ≥ 2 or KPS < 80%); however, more recently, even subtle differences in performance status (performance status = 0 versus 1) have been noted to predict significantly for survival.47 Of the ten studies listed in Table 1, performance status was identified as a significant factor (P = 0.07) in all but one. In that study,16 it was of borderline significance (P = 0.07). In one of the other studies,49 performance status was predictive of outcome in multivariate analysis but not univariate analysis. This finding probably reflects the heterogeneity of patients and patient populations. When this heterogeneity is taken into account (i.e., the effect of each factor is estimated with other factors in the model held constant), a more biologically meaningful estimate of the prognostic importance of each factor is revealed.15 Indeed, this phenomenon is seen with several other factors as well.16, 29

Because of the many contributing factors that may affect the prognosis of a patient, multivariate analysis is invaluable for determining which factors independently predict for survival. Of the representative studies listed in Table 1, 9 of the 10 contain some form of multivariate analysis. In these reports, performance status is the most consistently significant factor, with six of the studies identifying performance status as an independent prognostic indicator of outcome.14, 15, 29, 38, 47, 49 As depicted in Table 2, the hazards ratios reported for performance status are modestly predictive; however, when combined with other parameters, the predictive power of performance status increases dramatically.47

In addition to its impact on survival, performance status has been shown to predict the response to therapy in patients with hormone-refractory prostate cancer. Studies that evaluated investigative therapies for hormone-refractory prostate cancer demonstrated an increased response rate and duration of response in patients as a function of their performance status.14, 29 No threshold performance level was determined; rather, as performance status improved, so did the response rates. Therefore, performance status should be considered carefully when assessing response rates to new agents because even subtle biases in patient selection could alter the results.

**HEMOGLOBIN**

Similar to performance status, the level of plasma hemoglobin has been shown to be a prognostic factor for hormone-refractory prostate cancer. Despite differences in criteria for a low hemoglobin level, six of the nine studies that evaluated hemoglobin as a prognostic factor found that lower levels were associated with a poorer prognosis by univari-

### Table 2. Hazards Risk Ratios of Prognostic Factors

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Studies</th>
<th>Hazards Risk Ratios (95% confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>Stridhara, et al^46</td>
<td>2.5 (1.046-6.052)</td>
</tr>
<tr>
<td></td>
<td>Pienta, et al^27</td>
<td>1.91 (1.004-3.631)</td>
</tr>
<tr>
<td></td>
<td>Smith, et al^29</td>
<td>2.22 (1.38-3.57)</td>
</tr>
<tr>
<td></td>
<td>Kantoff, et al^*</td>
<td>1.93 (1.41-2.65)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Stridhara, et al^46</td>
<td>2.22 (1.19-4.15)</td>
</tr>
<tr>
<td>Performance status ≥ 2 and hemoglobin &lt;10 g/dL</td>
<td>Smith, et al^47</td>
<td>2.123 (1.279-3.525)</td>
</tr>
<tr>
<td>Weight loss (&lt;5%)</td>
<td>Kantoff, et al^*</td>
<td>1.63 (1.14-2.34)</td>
</tr>
<tr>
<td>Weight loss (&gt;5%)</td>
<td></td>
<td>1.97 (1.33-2.93)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>Stridhara, et al^46</td>
<td>1.857 (1.095-3.008)</td>
</tr>
<tr>
<td>In (LDH)</td>
<td>Kelly, et al^27</td>
<td>3.0 (1.7-5.1)</td>
</tr>
<tr>
<td>50% Decline in PSA</td>
<td>Kelly, et al^27</td>
<td>8.2 (2.6-26.0)</td>
</tr>
<tr>
<td></td>
<td>Smith, et al^47</td>
<td>2.20 (1.21-4.00)</td>
</tr>
</tbody>
</table>

^*Personal communication
ate analysis (Table 1). Because numerous variables can affect the hemoglobin level, including the extent of disease (i.e., anemia from marrow involvement), anemia from other chronic diseases, poor nutritional status, prior therapies such as radiotherapy or chemotherapy, and leukoerythroblastic anemia, a condition that occurs in 28% to 56% of patients with metastatic osseous lesions from prostate cancer, multivariate analysis is useful to evaluate the independent contribution of hemoglobin as a prognostic indicator.

At least eight studies have addressed the significance of hemoglobin by multivariate analysis. Of these, four studies have found it to be independently predictive of outcome. Conversely, in the study by Smith and co-workers, the prognostic significance of hemoglobin correlated with performance status such that, by pairwise interaction, hemoglobin levels less than 10 g/dL were significant only when the performance status was 2 or greater. In these patients with a poor performance status, the risk for death was 5.62 times higher if the hemoglobin level was less than 10 g/dL versus greater than 10 g/dL. Similarly, Fossa and co-workers demonstrated a significantly worse prognosis in patients with low hemoglobin (< 12 g/dL) levels and either a high baseline PSA (> 100 g/dL) or a high level of fatigue (as assessed by the patient). Thus, when considered independently or coupled with other prognostic factors, low hemoglobin levels seem to predict generally for a worse prognosis.

**LACTATE DEHYDROGENASE**

Lactate dehydrogenase (LDH) is a cellular enzyme released into the serum of patients from various tissues, particularly the liver. As a consequence of metastatic prostate cancer, elevated levels of LDH develop in many patients. Therefore, as a marker of metastatic visceral disease, serum enzymes including LDH have been evaluated. In one of the earliest studies showing the prognostic significance of this marker, Berry and co-workers demonstrated that abnormal serum levels of LDH and serum glutamic oxaloacetic transaminase (SGOT) correlated with a worse prognosis. Interestingly, these enzyme elevations did not correspond to overt liver metastasis because approximately 75% of the patients with elevated LDH had normal scans. It is possible that these enzyme elevations reflect otherwise subclinical liver disease or are predictive of a worse prognosis for other reasons. Regardless of their cause, abnormal serum levels of LDH and SGOT have been studied by numerous investigators for their prognostic significance.

In the study by Petrylak and co-workers, elevations in LDH, SGOT, and the presence of liver metastases were all poor prognostic indicators by univariate analysis, and only a log increase in LDH was found to be independently prognostic. Likewise, Kelly and colleagues found that although both SGOT and LDH were significant univariate prognostic factors, only the logarithm LDH was a significant independent prognostic indicator. These investigators validated their findings on an independent data set. The findings were corroborated by Sridhara and co-workers who established similar conclusions regarding LDH by multivariate analysis. Therefore, LDH, rather than SGOT or other more specific measurements of hepatic disease, is a likely independent predictor of prognosis in patients with prostate cancer.

Visceral organ involvement, and more specifically hepatic metastases, are not necessarily indicators of a worse prognosis. Because this pattern of spread is much less common, the diagnosis of prostate cancer in many of these patients is delayed. This lead time bias coupled with anecdotal experiences has led to the argument by some researchers that visceral (or measurable) metastases of prostate cancer behave differently than skeletal metastases. Although univariate analysis in several studies suggests these visceral patterns may be associated with a worse prognosis, careful multivariate analyses support similar response and survival rates in patients with visceral and skeletal disease.

**PROSTATE-SPECIFIC ANTIGEN**

Over the past decade, PSA has evolved into the most useful tumor marker for prostate...
cancer. As such, PSA has been validated as a marker of treatment failure following local therapy with surgery or radiation, of tumor response following hormonal therapy, and of tumor progression in the hormone-refractory state. This last use has led several investigators to evaluate the significance of PSA as a prognostic factor in patients with hormone-refractory prostate cancer.

Initially, several groups attempted to establish a threshold level above which PSA would predict for a worse prognosis. Of these investigators, Fossa and co-workers reported in 1992 that patients with hormone-refractory disease who had serum levels of PSA greater than 100 ng/mL prior to initiating therapy (pretreatment) had a significant decrease in survival by multivariate analysis. In addition, patients with a combination of an elevated pretreatment PSA level of greater than 100 ng/mL and a serum hemoglobin level less than 12 g/dL had a significantly higher mortality rate at 6 months. Meanwhile, Sridhara and co-workers found pretreatment levels greater than 176 ng/mL were a weak prognostic factor by multivariate analysis. In contrast, other groups found no prognostic significance of initial PSA levels, including threshold levels greater than 100 ng/mL. Most recently, a multi-institutional CALGB randomized study comparing mitoxantrone and hydrocortisone with hydrocortisone alone in which the median pretreatment serum PSA level was 150 ng/mL revealed that elevated pretreatment serum PSA levels above this median value were predictive of a poor survival (Table 2) (P.W. Kantoff, MD, personal communication). Thus, as a marker for volume of disease, PSA is relevant, yet there is no single threshold level that is reproducibly prognostic of survival.

Concurrent to these analyses of pretreatment PSA in hormone-refractory prostate cancer, several groups evaluated relative changes in PSA using landmark analysis to determine whether a certain percentage change in PSA was predictive of response to treatment. Although initial trials suggested a 75% decrease in PSA by 8 weeks was needed to increase survival and a threshold of greater than an 80% decline in PSA to correlate with response, Kelly and co-workers reported a dramatic survival advantage in patients with hormone-refractory prostate cancer who achieved a reproducible 50% decline in their PSA following initiation of therapy (Table 2). These results have received temperate support in other studies, including one by Smith and co-workers who showed that the 8-week time point was most significant. Alternatively, Sridhara and co-workers demonstrated no significant increase in the survival of patients who experienced more than 50% or more than 75% decrease in PSA by 4 weeks in two phase I studies of suramin. In an attempt to explain these discrepancies, investigators have suggested that the different time points (4 weeks versus 60 days), various investigational agents (which could affect PSA production independent of cytotoxicity), and statistical differences all could account for the seemingly paradoxical results. Caution must be advised in placing too much significance on PSA levels because changes in its expression or release could effect serum levels that do not correlate with disease response or survival. Therefore, many investigators still insist on traditional measurements of tumor response and survival when investigating new agents.

Other evaluations of PSA have been studied, such as its rate of rise and detection by reverse transcription-polymerase chain reaction (RT-PCR). One group from Chiba University in Japan has used the doubling time of serum PSA and prostatic acid phosphatase levels to predict for response. Interestingly, the PSA doubling time was tenfold greater in hormone-naïve patients than in patients with hormone-refractory prostate cancer; furthermore, patients with hormone-refractory prostate cancer with bone only disease had a lower median doubling time in comparison with patients with local or lymph node recurrences. Nonetheless, in patients with hormone-refractory prostate cancer, a serum PSA doubling time of greater than 80 days was associated with a better prognosis. In addition, with respect to serum detection of PSA by enzyme-linked immunosorbent (ELISA) assays versus RT-PCR, one study found that the presence of detectable PSA mRNA in the peripheral blood of patients with hormone-
refractory prostate cancer on the basis of RT-PCR predicted for poor survival, whereas serum PSA levels detected by ELISA did not. Although both of these studies need to be validated further, they add insight into the proliferation of hormone-refractory prostate cancer and its prognosis.

In addition to performance status, plasma hemoglobin, serum LDH, and PSA levels, many other parameters have been evaluated with mixed results (Table 1). Although there may be some prognostic significance underlying one or more of these other parameters, no clear patterns have emerged.

OTHER FACTORS

As is true for performance status and serum hemoglobin levels, weight loss, serum albumin, patient age, and race are factors that pertain to the description and condition of the host; however, unlike the first two factors, none of the next listed four factors have shown any consistently predictive pattern across studies. Perhaps the most promising of these factors has been weight loss. Two early studies identified weight loss, anorexia, or related entities to be independently prognostic (Table 1), whereas the CALGB group also identified even small changes in weight to be significant (Table 2) (P.W. Kantoff, MD, personal communication). Nonetheless, this variable has not been studied extensively, and the functional significance of weight loss remains unclear. It is not known whether aggressive supportive measures to control weight loss could affect survival in this population.

As mentioned previously, many potential prognostic indicators relate to the extent or volume of disease. Like serum PSA and LDH levels, prostatic acid phosphatase, alkaline phosphatase, and documentation of specific sites of disease by radiographic studies, including bone scans, CT, and radiography, have been evaluated. Because of their overlapping implications, many of these factors have proven redundant and thus are not significant by multivariate analysis. Included in this group is prostatic alkaline phosphatase, which may add some prognostic information in cases in which it changes discordantly with PSA but otherwise is of little additional value. Quantification of bone metastases and their extent have been evaluated by serum alkaline phosphatase, bone scans, and the presence of bone pain. Many of these studies offer promising results with univariate analysis but conflicting data by multivariate analysis, mostly because they each evaluate a different set of covariables. Nonetheless, new quantitative methods and technologies are promising in their ability to assess tumor volume. In addition, one provocative study has found that the early onset of pain (<1 year after the progression to hormone-refractory disease) predicts for a worse prognosis irrespective of the extent of disease. Unfortunately, this study was retrospective, nonrandomized, and small. Ultimately, these parameters will need to be validated prospectively in a randomized manner.

DISCUSSION

Prognostic indicators could have a tremendous impact on the management of patients with hormone-refractory prostate cancer. Currently, several factors have been correlated with survival based on a number of studies; however, these factors need to be corroborated in the context of prospective randomized trials. One of the problems in hormone-refractory prostate cancer has been the lack of multicenter phase III trials because few agents have shown enough promise to justify such a study. Recently, CALGB concluded one such study in which performance status, weight loss, and pretreatment PSA were predictive of survival. As further phase III studies are undertaken, more factors and combinations should be evaluated.

Prognostic factors such as performance status, hemoglobin, and serum PSA can help to identify patients who are likely to have a prolonged survival or to respond to therapy, but they do not identify patients who are likely to respond to certain treatments. Therefore, as more specifically targeted treatment options emerge for patients with hormone-refractory prostate cancer, prognostic factors
that predict which patients are appropriate for these treatments are needed. One such example of a specific prognostic factor and its treatment is HER2/neu amplification in breast cancer and the anti-p185HER2 monoclonal antibody; the presence of the HER2/neu oncogene predicts not only for a worse prognosis but also for sensitivity to this antibody. Similar targets and treatments are being evaluated in hormone-refractory prostate cancer, but because of the difficulty in obtaining fresh tissue from patients, the association of such targets with prognosis is not yet clear. In the future, such prognostic factors may represent the molecular phenotype of tumors that dictates patient care.

References


Address reprint requests to
Philip W. Kantoff, MD
Lank Center for Genitourinary Oncology
1230 Dana Building
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115