Use of Human Prostate-specific Antigen in Monitoring Prostate Cancer

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ABSTRACT

The newly reported human prostate-specific antigen (PA) is a specific histiotypic product of human prostate. With the use of a sensitive enzyme immunoassay, the circulating PA in prostatic cancer patients has been evaluated clinically. In 96 patients with advanced stage of disease (D2) and receiving chemotherapies, the pretreatment serum PA levels were found to be of prognostic value with regard to the patient survival. Ten patients with metastatic prostate cancer were monitored for more than 32 weeks by 183 serial PA values and were found generally to respond to the treatment. Additionally, another group of 32 patients who underwent curative therapies for localized prostate cancer, 161 serum samples were evaluated during periods of 12 to 114 weeks (average 56 weeks). Of these patients, five developed metastases during follow-up, and all were shown to exhibit increasingly elevated PA values, either corresponding to or preceding the clinical diagnosis of disease recurrence. These results suggest that PA is a new marker with potential value to merit further clinical study.

INTRODUCTION

To develop a procedure for immunochemical diagnosis of prostate cancer, we have identified and isolated a PA, which is distinct from prostatic acid phosphatase (13). With the use of an immunocytochemical procedure with the specific anti-PA antiserum, both primary and secondary tumors were shown to express PA, whereas the tumor of nonprostatic origin did not react with anti-PA serum (6). Specificity of PA was assessed further by several immunological procedures. PA was localized within prostatic ductal epithelial cells. Cell lines of malignant prostate origin retained the expression of PA and released the antigen in vitro into the culture fluid and in vivo into the circulation of athymic mice bearing prostate tumor (7).

These findings prompted us to develop an enzyme-linked immunoabsorbent assay for quantitation of circulating PA with a sensitivity of 0.10 ng of PA per ml of serum (3, 4).

Elevated levels of circulating PA were found in patients with prostatic cancer. Serum-borne PA was shown to be identical to that in the prostate (8). As a continuous study of PA, this report describes our preliminary study, which suggests the potential role of serum PA in monitoring prostatic cancer patients under therapy.

MATERIALS AND METHODS

Specimens. Sera were obtained from patients with histologically confirmed prostate cancer. Patients were staged clinically or surgically on the basis of lymph node dissection and other evaluations (12, 14). The criteria of the NPCP were used to determine the response to treatment (5). Patients were under various treatment protocols of the NPCP (10), including 106 patients in advanced stage of disease (D2) and receiving chemotherapies and 32 patients who underwent curative therapies.

Materials and Methods. Purification of PA, production of anti-PA serum, and specificity of the antiserum have been reported previously (6, 7, 13). Quantitation of serum PA by a sandwich-type enzyme immunoassay and the accuracy and reproducibility of this assay were recently reported (3). The sensitivity of the PA assay was 0.10 ng PA per ml serum (3).

Prognostic and Monitoring Applications of Serum PA in Prostate Cancer. In a group of 96 patients with advanced stage prostate cancer (D2) who were unresponsive to prior hormonal therapies and randomized to NPCP chemotherapies (10), serum PA levels were measured before treatments. All patients succumbed eventually to their disease. Forty patients survived for less than 20 weeks, 44 patients, survived 21 to 50 weeks, and only 12 patients survived for more than 51 weeks after the initiation of treatments.

Additionally, in another 10 patients in advanced stage of disease and receiving chemotherapies, serum PA assays were performed on 183 specimens, which were collected serially over a 32-week period (average, 90 weeks), and a clinicopathological evaluation was analyzed (5).

In another group of 32 patients with localized prostate cancer who underwent curative therapies (12 with radical prostatectomy and 20 with radiotherapy), 161 serum samples were analyzed; these were collected for 12 to 114 weeks, with an average of 56 weeks, for monitoring the disease recurrence. Five patients developed metastases during follow-up as confirmed by radiographic and radionuclide examinations as well as laboratory tests in accordance with criteria of the NPCP (5).

Statistical Analysis. Student's t test and $\chi^2$ analysis were used to evaluate the data. In addition, log-rank test of survival curve was used in evaluation of prognostic significance of the pretreatment levels of serum PA (1).
RESULTS

Pretreatment PA Values and Survival of Patients. In 96 patients with advanced prostate cancer who received chemotherapies, the serum level of PA before the administration of therapy was compared with the length of survival time in weeks. These 96 patients were divided into 3 groups based upon their pretreatment PA levels. As shown in Chart 1, the lower the pretreatment PA level the longer was their survival. The difference of survival time between Group 1 and Group 3 was highly significant ($p < 0.01$). Although no significant difference was found between Groups 1 and 2 or between Groups 2 and 3, the mean and median survival time showed a constant trend of longer survival with a lower initial PA value. Further, in 16 patients of Group 1 who had a normal or slightly elevated PA level, 44% of the deaths were delayed beyond when they otherwise would have occurred in comparison with Group 3. If the upper normal range of PA (3), 1.8 ng/ml, was used in analysis of the survival data, patients with normal pretreatment PA were found to have a statistically significantly longer survival time ($p < 0.01$) than all others combined.

Serial PA in Monitoring Prostate Cancer. The possible value of serum PA as a monitor for prostate cancer was evaluated in a group of 10 patients with metastatic disease who were receiving hormonal or chemotherapies and in another group of 32 patients who underwent curative therapies for localized disease. Prior to randomization into NPCP treatment protocols, all 10 patients were either stable or in progression of their prostate cancer. During the follow-up period, a total of 183 serum samples, serially collected for over 32 weeks, were analyzed for PA. Each patient had at least 10 serial specimens collected. PA levels were compared with the disease status of the patient in terms of treatment response. As summarized in Table 1, clinicopathological evaluation revealed a correspondence between clinical course and serum PA levels, i.e., using the patient as his own reference, PA level increased as disease progressed, decreased as disease regressed, and remained fluctuating when the patient was stable (11).

In another study involving 32 patients with localized prostate cancer who underwent curative therapy, a total of 161 serum samples were evaluated for PA during a period of 12 to 114 weeks (average, 56 weeks). Of these patients, 5 developed metastasis during follow-up and all 5 exhibited increasingly elevated PA values. As shown in Chart 2, the elevation of serum PA was detected 68 weeks preceding the clinical diagnosis of disease recurrence in one patient (Patient 3) and at the time of clinical detection of recurrence in 4 patients. PA value in 2 patients (Patients 2 and 5) never decreased to a normal range although both had a curative therapy, which may be suggestive of the presence of residual disease.

DISCUSSION

This report describes an initial clinical study of our enzyme immunoassay for monitoring serum PA in patients with prostate cancer. As communicated previously (3, 4), this assay is a reliable and reproducible procedure, inasmuch as it yields a coefficient of variation of 5.7% in 4 different ranges of PA. Further, the assay is sensitive enough to detect 0.10 ng of PA per ml of serum. Therefore, the possible use of serum PA in prognosis and monitoring of prostate cancer has been evaluated in this report.

In a group of 96 patients with metastatic prostate cancer who had failed to respond to previous hormonal therapy and

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment$^a$</th>
<th>Period of follow-up (wk)/no. of PA assayed</th>
<th>Response$^b$</th>
<th>PA value during therapy (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EST + VIN $\rightarrow$ Estradurin + PSL + RT</td>
<td>47/18</td>
<td>Clinical</td>
<td>Pretherapy</td>
</tr>
<tr>
<td>2</td>
<td>DES $\rightarrow$ DES + RT</td>
<td>86/11</td>
<td>S $\rightarrow$ P</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>DES $\rightarrow$ CYT</td>
<td>71/14</td>
<td>P $\rightarrow$ S</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>EST + VIN $\rightarrow$ PSL</td>
<td>32/14</td>
<td>P $\rightarrow$ S</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>DTIC $\rightarrow$ CYT $\rightarrow$ PSL</td>
<td>65/21</td>
<td>P $\rightarrow$ S $\rightarrow$ R</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>CYT + EST</td>
<td>82/19</td>
<td>P $\rightarrow$ R</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>DES</td>
<td>83/14</td>
<td>P $\rightarrow$ R</td>
<td>17</td>
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<td>8</td>
<td>EST $\rightarrow$ Streptozotocin</td>
<td>219/37</td>
<td>P $\rightarrow$ R</td>
<td>9.6</td>
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<tr>
<td>9</td>
<td>CYT + EST</td>
<td>72/11</td>
<td>C $\rightarrow$ R</td>
<td>S $\rightarrow$ P</td>
</tr>
<tr>
<td>10</td>
<td>DES + CYT</td>
<td>127/24</td>
<td>C $\rightarrow$ P</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ EST, estracyt; VIN, vincristine; DES, diethylstilbestrol; CYT, Cytoxin; DTIC, dimethyl-1-triazenoimidazole-4-carboxamide; PSL, prednisolone; RT, radiation therapy (10).

$^b$ Clinical treatment response: P, progression; S, stable; R, partial regression; C, complete regression; +, PA levels corresponding to treatment response (5).
that the following factors are associated with a poor prognosis were randomized into various chemotherapy protocols of the NPCP, pretreatment levels of serum PA have been shown to be of prognostic significance with regard to survival time of these patients. The lower the PA level, the longer is patient survival regardless of treatment regimens. It has been reported that the following factors are associated with a poor prognosis in prostate cancer: age, >70; hemoglobins, <12 mg/100 ml; body weight, <130 lb; partial or total confinement to bed; hydronephrosis; and elevated serum acid phosphatase activity (assayed by nonspecific chemical method) (2). However, none of these parameters are prostate or prostate cancer specific. Furthermore, a recent report indicates that neither single nor combined factors are useful in identifying long-term surviving patients with Stage D prostate cancer (9). Since PA is a prostate-specific protein and is expressed by both primary and secondary prostate tumors, it may be a valuable indicator in assessing the survival of the patient, as revealed in this study.

The results obtained with the serum PA levels in monitoring prostate cancer are encouraging. Serial PA levels have been found to correspond generally to clinical status in patients with Stage D2 disease and receiving treatment. In addition, serum PA detects disease progression in another group of patients with localized disease who had curative therapy. During follow-up, persistent and increasingly elevated PA levels were demonstrated in patients who developed metastases. These data suggest that progressively elevated PA levels show a good probability of the presence of recurrent disease. Certainly, more studies will be needed to determine the definitive clinical use in monitoring treatment response and detecting disease recurrence.

In summary, data have been presented to demonstrate the possible clinical use of serum PA with a view toward obtaining more information as to ultimate reliability of PA as a new marker for prostate cancer. The results presented in this report along with those communicated previously (3, 6–8) are of sufficient value to merit further clinical study.

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