Low Serum Testosterone Level Predicts Worse Response to Endocrine Therapy in Japanese Patients with Metastatic Prostate Cancer

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Abstract. Patients with prostate cancer generally respond to androgen withdrawal therapy, but progression to androgen-independence is frequently observed later. To examine whether pretreatment serum androgen status could predict disease progression in metastatic prostate cancer, pretreatment serum testosterone, histological grade, extent of bony metastasis, serum prostate-specific antigen (PSA) response to hormone therapy, and prognosis of the 40 patients with untreated metastatic prostate cancer who received endocrine therapy were evaluated. Although there were no differences in age, pretreatment PSA level, extent of bony disease and histological grade between patients with normal testosterone and those with low testosterone, PSA response after endocrine therapy was better in normal testosterone group. There was a significantly longer interval to disease progression in patients with normal testosterone than in those with low testosterone. The patients with metastatic prostate cancer with low serum testosterone were in the high risk group of worse response to endocrine therapy. Additional therapy might be considered in those patients.

Key Words: Prostate cancer, Testosterone, Prognosis

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APPROXIMATELY 80% of advanced prostate cancer patients respond to endocrine therapy at the start of treatment [1]. Prostate cancer growth is stimulated in the presence of androgen, while androgen deprivation causes prompt regression of tumor volume [1]. Indeed, it is the induction of apoptosis of the androgen dependent prostate cancer cells, which is the basis for the therapeutically beneficial response to androgen withdrawal therapy [2]. Since the majority of patients will ultimately relapse and die of progressive disease [3], it would be very helpful if it were possible to identify which patients would respond to androgen withdrawal therapy at the initial treatment.

Androgen plays a key role in the etiology of prostate cancer based on the observation that men castrated prior puberty and those with 5α-reductase deficiency do not develop prostate cancer [4]. A number of studies have evaluated the potential diagnostic and prognostic value of serum testosterone determination in prostate cancer patients although the data are conflicting [5–10]. In order to examine whether prostate cancer in men with low testosterone may differ from prostate cancer in those with normal testosterone level, patients who had been treated with endocrine therapy were investigated. In this study, we showed prostate cancer in men with low testosterone had worse response to androgen withdrawal therapy.

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Materials and Methods

Patients

Forty patients with untreated metastatic prostate cancer who received hormone therapy between 1988-1999 at Toyama Medical and Pharmaceutical University Hospital were included in the present study. Age distribution ranged from 59 to 87 years, with a mean ± SD of 73.1±7.1. The follow-up period was 3 to 156 months (mean ± SD: 28.8±28.0 months). All the patients underwent surgical (14 cases) or medical (26 cases) castration (Table 1). In those patients surgically castrated 5 and 9 patients were administrated chlormadinone acetate and diethylstilbestrol diphosphate, respectively. In the medically castrated group, all patients were injected with luteinizing hormone-releasing hormone analogue and 6, 6, 4 and 2 patients were additionally administered chlormadinone acetate, diethylstilbestrol diphosphate, flutamide and bicalutamide, respectively.

Measurements

Histological grade of the tumor was evaluated according to the classification of Gleason [11]. The extent of bone metastasis was classified according to the method described by Soloway et al. [12]. Bone scintigraphy was performed in all patients. PSA determination, digital rectal examination (DRE), transrectal ultrasonography (TRUS), chest and pelvic X-p, computed tomography (CT) and cystoscopy were performed in all patients. The T factor, according to the TNM classification [13], was T2 in one patient, T3 in 31 patients and T4 in eight patients. The sites of distant metastasis were bone in 36 patients, lymph node in seven patients (five of whom had bone metastases) and bladder metastasis in eight patients (five of whom had bone metastases). Phlebotomy was performed between 6:00-8:00 AM before digital rectal examination or other prostatic manipulation. PSA was measured using a Tosoh II PA kit (Tosoh Corp, Tokyo, Japan). Testosterone was determined by a radioimmunoassay (Nippon DPC, Chiba, Japan). The short-term response of tumor markers was estimated 3 months after the commencement of therapy by change in serum PSA: complete response (CR), normalization; partial response (PR), more than 50% decrease from pretreatment level; progressive disease (PD), more than 25% increase from pretreatment level; and no change (NC), between PR and PD. PSA determination, DRE and plain pelvic X-p were performed every three months. Bone scintigraphy and TRUS were performed every one year. Once clinical progression was suspected by PSA and/or DRE, bone scintigraphy, TRUS, pelvic CT, and magnetic resonance imaging were performed. Clinical progression following endocrine therapy was defined as the appearance of at least one of the following: new or worsened bone metastasis, and more than 25% increase in local or soft tissue disease. PSA failure alone was not considered as disease progression.

Statistical analysis

Cause-specific and disease-free survival was calculated by the Kaplan-Meier method [14]. Values from patients with normal testosterone and with low testosterone were compared using the Mann-Whitney U-test for non parametric analyses, and p<0.05 was considered statistically significant.

Table 1. Treatment modalities stratified by pretreatment serum testosterone level

<table>
<thead>
<tr>
<th>Treatment</th>
<th>≥3.0 ng/ml</th>
<th>&lt;3.0 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castration + CMA</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Castration + DES</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>LHRH</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>LHRH + CMA</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>LHRH + DES</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>LHRH + flutamide</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>LHRH + bicalutamide</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CMA: chlormadinone acetate; DES: diethylstilbestrol diphosphate; LHRH: luteinizing hormone-releasing hormone analogue

Results

Mean total serum testosterone level was 4.3±1.7 ng/ml (Table 2), which is equivalent to the previous study measured in Australia using same kit [9, 10]. There was no association between age and serum testosterone level (p=0.29, Spearman rank correlation). Men with a serum total testosterone value of <3.0 ng/ml were defined as low testosterone accord-
Table 2. Characteristics of patients with low testosterone versus those with normal testosterone levels.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 40)</th>
<th>Low testosterone (n = 11)*</th>
<th>Normal testosterone (n = 29)</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.1 ± 7.1</td>
<td>71.4 ± 8.7</td>
<td>73.8 ± 6.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>432 ± 689</td>
<td>251 ± 276</td>
<td>500 ± 786</td>
<td>n.s.</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>4.3 ± 1.7</td>
<td>2.5 ± 0.4</td>
<td>4.9 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gleason score</td>
<td>7.2 ± 1.4</td>
<td>7.1 ± 1.2</td>
<td>7.3 ± 1.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>1.9 ± 1.1</td>
<td>2.1 ± 0.8</td>
<td>1.9 ± 1.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Pretreatment serum testosterone < 3.0 ng/ml
b Difference between those with low versus normal serum testosterone values. n.s., not significant.

...ing to the previous reports [10, 15, 16]. Modalities of endocrine treatment stratified by pretreatment testosterone level were shown in Table 1. There were no statistically significant differences of treatment modalities (i.e. surgical vs medical castration, use of estrogen/antiandrogen) between normal (i.e. ≥3.0 ng/ml) and low testosterone groups. There were no differences in patient’s age, serum PSA level, extent of bony disease and Gleason score between two groups (Table 2). Three months after the start of endocrine therapy, PSA value in 26 patients had decreased to below the normal limit, whereas that in 14 patients was above 4.0 ng/ml. There was a statistically significant association between serum testosterone and PSA response (Table 3). Mean testosterone level was 4.7 ± 1.7 ng/ml in the CR group and 3.5 ± 1.1 in the PR/NC group (p = 0.022). To examine the influence of pretreatment serum testosterone on the disease progression, progression-free survival according to testosterone was evaluated (Fig. 1). There was a significantly longer interval to disease progression in patients with a normal testosterone than in those with low testosterone. Cancer-specific survival in patients with a pretreatment normal testosterone seemed to be better than those with low testosterone (Fig. 2), although the difference was not statistically significant (p = 0.051). When the patients were stratified by the use of estrogen or antiandrogen, there were no significant differences in progression-free and cancer-specific survivals.

Table 3. Association between pretreatment serum testosterone and PSA response 3 months after the endocrine therapy.

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>CR*</th>
<th>PSA</th>
<th>Response PR/NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0 ng/ml</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>≥3.0 ng/ml</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.0021, Chi-square test for trend.
* Definition of CR/ PR/NC was described in “Materials and Methods”.

Discussion

Testosterone is a predominant androgen in men [17]. It is secreted by Leydig cells in response to luteinizing hormone secreted by a normally functioning hypothalamic-pituitary-gonadal axis [17]. The association of serum testosterone with prostate cancer is incompletely understood. While androgenic stimulation is needed for the development and growth of prostate, testosterone levels have failed to distinguish benign from malignant process [5-7]. On the other hand, men with prostate cancer are reported to have higher testosterone level than patients with benign prostatic hyperplasia [8]. Studies comparing serum testosterone in men with and without prostate cancer have produced widely varying results [5-9]. The association of serum testosterone and tumor progression in prostate cancer has been also conflicting. Hoffman et al. reported that low free serum testosterone may be a marker of more aggressive prostate cancer based on a higher percent of positive biopsy cores and high rate of tumors with a Gleason score of
8 or greater in patients with low free testosterone [18]. On the other hand, Mikkola et al. reported that pretreatment testosterone level in patients without metastatic prostate cancer was not higher than those with metastasis [19]. The conflicting results might be due to the differences in selection of controls, inclusion of patients with different stages of prostate cancer, and time of hormone determination.

Low serum testosterone has been identified as a poor prognostic factor in men with metastatic prostate cancer [20-22]. A preexisting low serum testosterone level might selectively affect growth of less androgen-dependent cancer cells, which might be more resistant to subsequent androgen withdrawal. To our knowledge, reports of the association of serum testosterone and the disease prognosis besides

Fig. 1. Progression-free survival according to the pretreatment serum testosterone level. p=0.034.

Fig. 2. Cancer-specific survival according to the pretreatment serum testosterone level. p=0.051.
those of the Western countries are very limited. The present study confirmed the previous findings [20-22]. The reports describing the correlation between serum testosterone and PSA response after androgen therapy in patients with metastatic prostate cancer are also limited. The secretion and production of PSA are under androgenic control [23]. However, it has been difficult to demonstrate a correlation of androgen with PSA [16]. The present study showed no effect of pretreatment serum testosterone on PSA since PSA levels in patients with low testosterone were not statistically different from those with normal testosterone level. Androgen dependent changes in the prostate might be detectable only at the low end of serum testosterone. However, PSA response 3 months after the endocrine therapy was significantly better in patients with a normal testosterone than those with low testosterone levels.

Pretreatment testosterone level was not identified as a significant prognostic factor in 150 patients with metastatic prostate cancer treated with a nonsteroidal antiandrogen [15]. This discrepancy might be related to the different mode of action of the antiandrogen used. In the present study, serum testosterone level in all the patients after endocrine therapy was confirmed to be below the castrated level. Men with partial androgen deficiency as defined by total serum testosterone level of less than 3.0 ng/ml increase with age and are estimated to be in the range of 20% in elderly men [24]. The mechanism of the decline of testosterone with age is not fully understood. All levels of the hypothalamic-pituitary-gonadal hormone axis might be involved, predominantly at the testicular level [24]. Primary testicular changes as suggested by a decreased Leydig cell number and an impaired testicular perfusion might cause lower testosterone level [24]. Asians including Japanese have an incidence of prostate cancer 10 times lower than men in the US and in Northern Europe [25]. There is a possibility that Japanese have a lower serum testosterone level. The Dutch-Japanese case control study found that testosterone level was significantly lower in Japanese men compared to Dutch men [26]. In the present study serum testosterone level was equivalent to the previous reports [9, 10]. Further large-scale study is needed.

In conclusion, patients with metastatic prostate cancer with low serum testosterone were in the high risk group of worse response to endocrine therapy. Additional therapy should be considered for those patients.

References


