Serum Testosterone Level to Predict the Efficacy of Sequential Use of Antiandrogens as Second-line Treatment Following Androgen Deprivation Monotherapy in Patients with Castration-resistant Prostate Cancer

Kohei Hashimoto, Naoya Masumori*, Jiro Hashimoto, Akio Takayanagi, Fumimasa Fukuta and Taiji Tsukamoto

Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan

*For reprints and all correspondence: Naoya Masumori, Department of Urology, Sapporo Medical University School of Medicine, S1, W16, Chuo-ku, Sapporo 060-8543, Japan. E-mail: masumori@sapmed.ac.jp

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Objective: We investigated whether serum testosterone after the failure of androgen deprivation monotherapy predicted the efficacy of antiandrogens added to androgen deprivation monotherapy as second-line treatments for patients with castration-resistant prostate cancer.

Methods: We reviewed 30 patients with castration-resistant prostate cancer who received maximal androgen blockade with addition of an antiandrogen (delayed maximal androgen blockade) (bicalutamide 80 mg daily for 21 patients and flutamide 375 mg daily for 9 patients) as the second-line treatment. The patients were divided into two groups by serum testosterone before delayed maximal androgen blockade: 22 in the testosterone \( \geq 5 \) ng/dl group and 8 in the testosterone \(< 5 \) ng/dl group. A prostate-specific antigen response was defined as a prostate-specific antigen decline of \( \geq 50\% \) from the pre-treatment level.

Results: The response rate was significantly higher in the testosterone \( \geq 5 \) ng/dl group than in the testosterone \(< 5 \) ng/dl group (77.3 vs. 37.5\%, \( P = 0.04 \)). During the median follow-up period of 52.5 months, 24 patients (80.0\%) developed prostate-specific antigen progression. A serum testosterone level of \(< 5 \) ng/dl was an independent factor to predict prostate-specific antigen progression in a reduced and full model setting on multivariate analysis (hazard ratio 6.03, \( P = 0.003 \) and 5.99, \( P = 0.003 \), respectively). The 1-year prostate-specific antigen progression-free survival rate was significantly higher in the testosterone \( \geq 5 \) ng/dl group than in the testosterone \(< 5 \) ng/dl group (52.9 vs. 0\%, \( P = 0.002 \)), as was cause-specific survival (5 years: 66.0 vs. 33.3\%, \( P = 0.007 \)).

Conclusions: Serum testosterone could play an important role when delayed maximal androgen blockade is indicated as the second-line treatment in patients with castration-resistant prostate cancer. Delayed maximal androgen blockade might be more beneficial in patients with a serum testosterone level of \( \geq 5 \) ng/dl.

Key words: castration-resistant prostate cancer – maximal androgen blockade – antiandrogen – testosterone – prognosis

INTRODUCTION

Androgen deprivation monotherapy (ADMT) consisting of surgical or medical castration alone has been the mainstay first-line treatment for advanced prostate cancer. The response to this treatment lasts for a median of 36–48 months (1). However, in most cases, the disease progresses despite the castrate testosterone level and results in castration-resistant prostate cancer (CRPC). The treatment strategy for CRPC has not been established yet.

Maximal androgen blockade (MAB) adding an antiandrogen after the failure of ADMT, which is termed delayed MAB, is one of the treatment options for CRPC (1). The
aim of this treatment is to antagonize the actions of marginal amounts of androgens originating from the adrenal glands at the receptor level. We previously reported the efficacy of delayed MAB as the second-line treatment (2). The prostate-specific antigen (PSA) response rates of delayed MAB have been reported to range from 22 to 82% (2–10). These series found that the cause-specific survival in responders to the treatment was significantly better than that in non-responders. However, it remains unclear who can be expected to respond to delayed MAB.

In this study, we investigated whether the serum testosterone level after the failure of ADMT, mainly reflecting the androgens originating from the adrenal glands, predicted the efficacy of delayed MAB.

PATIENTS AND METHODS

Institutional review board approval was obtained for this study. We retrospectively analyzed 30 patients with CRPC who received delayed MAB with bicalutamide 80 mg daily or flutamide 375 mg daily as the second-line treatment at our institution between March 1999 and March 2008. All patients had serum PSA determination (ECLusys PSA II assay) before prostate biopsy. Systematic prostate biopsy was done using an 18 G needle under the guidance of transrectal ultrasound and 6–14 (median: 8) biopsy cores were taken from each patient. Clinical stage was determined by digital rectal examination, transrectal ultrasound, abdominal computed tomography, chest X-ray and bone scanning using 99mTc-methylene-diphosphonate. Stage and histological grade were assigned using the 2002 UICC-American Joint Committee on Cancer TNM system and the Gleason system, respectively.

All patients were treated according to our treatment strategy for advanced prostate cancer. As the first-line treatment, all patients were treated with ADMT, with surgical castration for 9 patients and the administration of a luteinizing hormone-releasing hormone (LHRH) agonist for 21 patients. As all patients had PSA progression during ADMT, despite the castrate testosterone level (<50 ng/dl), the second-line treatment was done using an additional antiandrogen in ADMT (delayed MAB). Three patients had clinical progression before delayed MAB. If PSA elevation developed during the delayed MAB, the antiandrogen was terminated and the patient was observed for antiandrogen withdrawal syndrome (AWS). If AWS was not found, an alternative antiandrogen, estrogen or glucocorticoids with ADMT were given as the third-line treatment. Drugs used in the second- or third-line treatment were decided based on the preferences of the physicians.

Physical examination and serum PSA measurement were performed every 3 months throughout the follow-up period. Digital rectal examination, transrectal ultrasonography, abdominal computed tomography, chest X-ray and bone scanning were performed when clinically indicated. A PSA response was defined as a PSA decline of 50% or greater from the PSA level at the start of the delayed MAB, and the treatment was evaluated to be effective. The time of PSA progression was defined as the first of three consecutive increases in the PSA level. The PSA doubling time (PSA-DT) was calculated by least-squares linear regression analysis (11), using three or more PSA determinations at the time from the failure of ADMT to the start of the delayed MAB. Positive AWS was defined as a PSA decline of 50% or greater from the PSA level at the time when the antiandrogen was discontinued. Cause-specific survival time from the failure of ADMT to death from prostate cancer was calculated.

Serum testosterone levels (ECLIA assay) were measured from stored serum just before and 3 months after delayed MAB. All patients were divided into two groups by the serum testosterone level before delayed MAB: ≥5 ng/dl (T ≥ 5 ng/dl group) and <5 ng/dl (T < 5 ng/dl group). Fisher’s exact test and the Mann–Whitney U-test were carried out to compare various clinical variables between the groups. The paired t-test was used to assess changes in the serum testosterone level after delayed MAB. PSA progression-free and cause-specific survival rates were calculated using the Kaplan–Meier method, and the differences in survival were assessed by the log-rank test. The Cox proportional hazards model was used to estimate the prognostic factors of PSA progression based on the optimal cut-off value in each parameter. A P-value of <0.05 was considered to be statistically significant. We used the computer program StatView 5.0 for Windows (SAS Institute, Cary, NC, USA) for statistical analysis.

RESULTS

The characteristics of patients according to the serum testosterone levels just before delayed MAB are shown in Table 1. The mean serum testosterone level was 9.3 ng/dl (median: 10 ng/dl, range: 2–41). Of the patients, 22 (73.3%) were in the T ≥ 5 ng/dl group and 8 (26.7%) in the T < 5 ng/dl group. There was no significant difference in variables between the two groups. Sixteen of the 22 patients (72.7%) in the T ≥ 5 ng/dl group had lymph node or distant metastasis, as did 7 (87.5%) of the 8 in the T < 5 ng/dl group. During the median follow-up period of 52.5 months, 24 patients (80.0%) developed PSA progression at a median of 11.0 months. Of the 30 patients, 14 (46.7%) and 1 (3.3%) died of prostate cancer and pneumonia, respectively.

We assessed changes in the serum testosterone level just before and 3 months after delayed MAB according to the additional antiandrogens. In the patients with bicalutamide, the serum testosterone level did not significantly change (mean: from 11.4 to 10.6 ng/dl, P = 0.52), whereas it clearly declined in those with flutamide (mean: from 15.9 to 4.4 ng/dl, P < 0.001).
The relationship between the serum testosterone level just before delayed MAB and the rate of PSA decline is shown in Fig. 1. A PSA response (≥50% PSA decline rate) was observed in 14 (66.7%) of 21 patients with bicalutamide and in 6 (66.7%) of 9 with flutamide. The response rate was significantly higher in the T ≥5 ng/dl group than in the T < 5 ng/dl group (77.3 vs. 37.5%, P = 0.04). In each T group, there was no significant difference in the response rates between bicalutamide and flutamide.

Univariate and multivariate Cox proportional hazards analysis was performed to evaluate factors that could predict PSA progression in delayed MAB (Table 2). All variables were collected after removal of confounding variables. Univariate analysis revealed that distant metastasis, time to progression during ADMT, PSA-DT after the failure of ADMT and a serum testosterone level just before delayed MAB were associated with PSA progression-free survival. However, the time to progression during ADMT of <12 months and a serum testosterone level of <5 ng/dl were the independent factors for PSA progression in a reduced model.
setting on multivariate analysis (hazard ratio 5.91, \( P = 0.005 \) and 6.03, \( P = 0.003 \), respectively). In addition, a serum testosterone level was also the only independent factor in the full model setting (hazard ratio 5.99, \( P = 0.003 \)).

The 1-year PSA progression-free survival rate was significantly higher in the T\( \geq \) 5 ng/dl group than in the T\(< 5 \) ng/dl group (52.9 vs. 0\%, \( P = 0.002 \)) (Fig. 2A). The 2- and 5-year cause-specific survival rates were 89.9 and 66.0\% in the T\( \geq \) 5 ng/dl group, respectively, whereas they were 50.0 and 33.3\% in the T\(< 5 \) ng/dl group (\( P = 0.007 \)), respectively (Fig. 2B).

**DISCUSSION**

CRPC has heterogeneous aspects based on biological status (6). Three different statuses can be identified as: (i) residual androgen-sensitive, the cancer cells are still sensitive to residual androgens of adrenal origin; (ii) hormone-sensitive, the disease is no longer androgen-sensitive but it may still be influenced by hormones; (iii) androgen- and hormone-refractory, the disease has become completely hormone-insensitive. Delayed MAB would be a reasonable option for CRPC with residual androgen sensitivity.

Actually, some patients with CRPC showing progression during ADMT are sensitive to marginal amounts of androgens originating from the adrenal glands. We previously reported the efficacy of delayed MAB in 53 patients with CRPC (2). A response to delayed MAB as the second-line treatment was found in 67.7\% of the patients with bicalutamide and 66.7\% of those with flutamide. In the present study, a response to delayed MAB was observed in 67\% of the patients with CRPC. The PSA response rates to bicalutamide and flutamide were comparable in delayed MAB. Several studies reported rates of efficacy of delayed MAB

Table 2. Univariate and multivariate Cox’s proportional hazards analysis of factors for predicting PSA progression in delayed MAB

<table>
<thead>
<tr>
<th>Category</th>
<th>Univariate</th>
<th>Multivariate(^a)</th>
<th>Multivariate(^b)</th>
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<tr>
<td></td>
<td>( P )</td>
<td>( HR )</td>
<td>95% CI</td>
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<td>Gleason score on biopsy</td>
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<td>0.49</td>
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<tr>
<td>Distant metastasis</td>
<td>absent vs. present</td>
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<td>Nadir PSA during ADMT (ng/ml)</td>
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<td>0.06</td>
</tr>
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<td>Time to progression during ADMT (months)</td>
<td>( \geq 12 ) vs. (&lt; 12 )</td>
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<td>0.07</td>
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<tr>
<td>PSA-DT after failure of ADMT (months)</td>
<td>( \geq 10 ) vs. (&lt; 10 )</td>
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<td>0.17</td>
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<tr>
<td>Serum testosterone just before delayed MAB (ng/dl)</td>
<td>( \geq 5 ) vs. (&lt; 5 )</td>
<td>0.005</td>
<td>0.003</td>
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<tr>
<td>Decline rate in serum testosterone during delayed MAB (%)</td>
<td>(&lt; 0 ) vs. ( \geq 0 )</td>
<td>0.44</td>
<td>0.33</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

\(^a\)Full model.

\(^b\)Reduced model.

Figure 2. PSA progression-free survival (A) and cause-specific survival (B) after delayed MAB according to the testosterone level before delayed MAB.
after the failure of ADMT similar to ours, ranging from 22 to 86% when adding bicalutamide (3–5,8,9) and from 20 to 80% for flutamide (3,4,6,7,10).

Factors for predicting the efficacy of delayed MAB after the failure of ADMT have been reported (7,8). Fujikawa et al. (7) found that a low nadir PSA level during the initial ADMT was most strongly correlated with a better prognosis of delayed MAB with flutamide. Fujii et al. (8) demonstrated that PSA-DT between the failure of ADMT and the start of delayed MAB was a factor predicting the efficacy of delayed MAB with bicalutamide. In the present study, although PSA-DT after the failure of ADMT also predicted the efficacy of delayed MAB in univariate analysis, the serum testosterone level just before delayed MAB was the only factor to predict PSA progression in both the full and reduced model setting on multivariate analysis. In addition, serum testosterone also predicted cause-specific survival. Thus, it is suggested that the serum testosterone level should be seriously considered when the next management is indicated for patients with CRPC.

The serum testosterone level might determine the aggressiveness of prostate cancer. In radical prostatectomy series, lower serum testosterone levels were reported to be associated with more advanced pathological features (12,13) and poorer prognosis (14). Likewise, in patients treated with MAB initially, low serum testosterone levels at baseline predicted worse treatment outcomes (15–17). In the present study, all patients with serum testosterone levels just before delayed MAB of <5 ng/dl showed PSA progression by 1 year. It was uncertain whether these patients had continuously had a low testosterone level since the time of the first-line ADMT. However, CRPC that progressed under a low testosterone level during ADMT may have already adapted to an androgen-independent environment. Since an additive effect of antiandrogens cannot be expected, estrogen therapy or chemotherapy with docetaxel should be considered as second-line treatments for such patients.

The serum testosterone level is maintained or elevated by pure non-steroidal antiandrogen monotherapy because blocking encephalic and peripheral androgen receptors by antiandrogens leads to the release of more LHRH (18–20). However, flutamide could suppress adrenal androgens in the limited conditions under castration. We found that the serum testosterone level declined in delayed MAB with flutamide, but not with bicalutamide. Some studies also reported that levels of serum adrenal androgens, including dehydroepiandrosterone sulfate, androstenedione and testosterone, declined in MAB with flutamide (21,22). This action of flutamide may be helpful to competitively antagonize androgen receptors more efficiently than bicalutamide. However, in the present study, there was no significant difference in the response rates to bicalutamide and flutamide. This result might be related to the retrospective nature of our study, because there were various differences in the numbers of patients and serum testosterone levels between patients taking bicalutamide and flutamide.

We identified an association between the serum testosterone level and the efficacy of delayed MAB. However, there are some limitations to this study, including its retrospective nature and the small number of patients. The serum testosterone level was not measured before ADMT. In addition, it was measured using sera obtained at various times from 9 a.m. to noon. It is unknown how these limitations affected the serum testosterone level and the outcome. However, this is the first study showing that the serum testosterone level potentially predicts the efficacy of adding an antiandrogen in delayed MAB. In the future, we need to conduct a prospective investigation to confirm the impact of additional antiandrogens on the prognosis of delayed MAB according to adrenal androgen levels.

**CONCLUSIONS**

We found that adding an antiandrogen as the second-line treatment could be suitable in patients with CRPC that progressed during ADMT. Delayed MAB would be more beneficial for patients with serum testosterone levels of ≥5 ng/dl.

**Conflict of interest statement**

None declared.

**References**