Effect of Delayed Maximal Androgen Blockade Therapy for Patients with Advanced Prostate Cancer Who Fail to Respond to Initial Androgen Deprivation Monotherapy

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Objectives: We analyzed the efficacy of additional antiandrogens as second- and third-line treatments after the failure of initial androgen deprivation monotherapy.

Methods: This retrospective study included 53 patients with advanced prostate cancer initially treated with androgen deprivation monotherapy alone. An antiandrogen was added to androgen deprivation monotherapy as the second-line treatment after the failure of the initial androgen deprivation monotherapy. Another antiandrogen, estrogen or steroid was given as the third-line treatment after the second-line treatment failed.

Results: The initial androgen deprivation monotherapy was effective in all 53 patients for a median of 9.6 months. Thirty-three (62.3\%) patients showed a prostate-specific antigen response to the second-line treatment for a median of 10.7 months. Of the 46 patients who received the third-line treatment, 16 (34.8\%) showed a prostate-specific antigen response for a median of 6.0 months. Patients who responded to the second-line treatment had a significantly higher cancer-specific survival rate than those without a response. In multivariate analysis, a nadir prostate-specific antigen of 4.0 ng/ml or greater during androgen deprivation monotherapy and prostate-specific antigen doubling time of less than 10 months after androgen deprivation monotherapy failure were independent risk factors for prostate cancer death after androgen deprivation monotherapy failure, with hazards ratios of 5.59 and 8.00, respectively. The 5-year cancer-specific survival rates were 100\%, 65.0\% and 15.5\% in patients with 0, 1 and 2 risk factors, respectively ($P = 0.047$).

Conclusions: In this study, the second- and third-line treatments were effective for patients with advanced prostate cancer. Nadir prostate-specific antigen during androgen deprivation monotherapy and prostate-specific antigen doubling time just after the failure of androgen deprivation monotherapy are factors that can predict the prognosis.

Key words: prostate cancer – delayed maximal androgen blockade therapy – androgen deprivation monotherapy – PSA doubling time – PSA nadir

INTRODUCTION

Androgen deprivation therapy (ADT) is the preferred treatment for advanced prostate cancer. After ADT by medical or surgical castration, the majority of patients initially show some evidence of a clinical response (1). However, the disease becomes refractory to hormone treatment in most patients. In those patients, a rising prostate-specific antigen (PSA) level is first observed, followed by progression of clinical symptoms (2).

Androgen deprivation monotherapy (ADMT) consisting of medical or surgical castration alone, or maximal androgen blockade (MAB) consisting of ADMT plus an antiandrogen,
is used to manage patients with advanced prostate cancer as the initial treatment. It is controversial whether MAB should be given initially because of the small survival benefit, adverse effects and cost (3–5). Moreover, the treatment strategy after the failure of the initial ADT is not fully established and there is no consensus about the time when the second-line treatment should be initiated, or which treatment is preferable among alternative antiandrogens, estrogens, steroids and docetaxel-based chemotherapy.

In this study, we analyzed the clinical courses of patients after the failure of the initial ADMT and evaluated the efficacy of additional antiandrogens as the second- and third-line treatments.

SUBJECTS AND METHODS

Patients
We retrospectively analyzed a total of 53 patients with advanced prostate cancer who were diagnosed at Sapporo Medical University Hospital and Sunagawa City Medical Center from 1994 to 2007. Clinical stage was evaluated according to the 1997 TNM classification. T stage was determined by digital rectal examination, computed tomography (CT) and/or transrectal ultrasonography. Pelvic lymph node metastasis was assessed by CT. Bone metastasis was assessed by bone x-ray and radioisotopic bone imaging using 99mTc-methylene-diphosphonate.

The mean age was 74 years (range: 50–83) and serum PSA ranged from 3.7 to 8190 ng/ml at the initial treatment. Gleason score of biopsy were 6 or less in 3 patients, 7 in 13 patients and 8–10 in 37 patients. Clinical stages were T3-4N0M0 in 12, cTanyN1M0 in 9 and TanyNanyM1 in 32 patients. The overall follow-up period from the start of treatment for prostate cancer to the last visit ranged from 8.2 to 147.9 months with a median of 59.1. The initial ADMT was effective in all 53 patients and the median time from the start of ADMT to its failure was 9.6 months (0.8–57.3). The median nadir PSA during the initial ADMT was 2.1 ng/ml (0.0–1230) and the median PSA at the failure of the initial ADMT was 3.1 ng/ml (0.2–1590). Failure was defined as described below.

TREATMENTS

Patients were all initially treated with ADMT by medical or surgical castration alone. Medical castration was achieved using a luteinizing hormone-releasing hormone agonist. Once ADMT failed, the second-line treatment with ADMT plus an antiandrogen was initiated. If the second-line treatment failed, the antiandrogen was terminated and antiandrogen withdrawal syndrome (AWS) was observed. When AWS was not found in the subsequent clinical course, another antiandrogen, estrogen or steroid with ADMT was given as the third-line treatment. Each drug used in the second- or third-line treatment was decided based on the preference of the physician.

EVALUATION OF RESPONSE AND DEFINITIONS OF TERMS

Changes in the post-therapy PSA level were defined according to the recommendations of the PSA Working Group (6). A ‘PSA response’ was defined as a 50% or greater decline in the pretreatment PSA level after therapy, and the treatment was evaluated to be effective. A less than 50% decline in the PSA level or a rising PSA level during the treatment was defined as ‘no PSA response’. When the PSA failure defined below was found during the treatment, the ongoing treatment was evaluated as having no efficacy. PSA failure was essentially defined as three consecutive increases in the PSA level. The time of PSA failure was defined as the first of the three consecutive increases in the PSA level. The PSA doubling time (PSA-DT) was calculated using the following formula: $PSA-DT = \log(2) \times t/\log(final PSA) - \log(initial PSA)$, where ‘log’ was the natural logarithm function and ‘t’ was the time from the initial level to the final PSA level (7). To calculate the PSA-DT after the initial ADMT failed, the initial PSA was defined as the PSA level at the time of failure of the initial ADMT, and the final PSA level was defined as the PSA value at the time of starting the second-line treatment. Positive AWS was defined as a 50% or greater decrease in the PSA level compared with that at the time when the antiandrogen was discontinued. Cause-specific survival time from the failure of the initial ADMT to death from prostate cancer was calculated.

STATISTICAL ANALYSIS

For the statistical analysis of data, the Kaplan–Meier method, log-rank test and Cox proportional hazards analysis were applied using StatView (SAS Institute, Cary, NC, USA). Statistical significance was defined as $P < 0.05$.

RESULTS

Bicalutamide 80 mg/day was used in 31 patients followed by flutamide 375 mg/day in 18 and chlormadinone acetate (CMA) 100 mg/day in 4. Of the 53 patients, 33 (62.3%) had a PSA response to the second-line treatment. The response was found in 67.7% of patients with bicalutamide treatment and 66.7 of those with flutamide. No patients responded to CMA treatment. The median PSA failure-free survival in the 33 patients having a PSA response was 10.7 months. Of these 33 patients, 5 remained free of any increase in the PSA level at the end of follow-up and 28 showed PSA failure of the second-line treatment. No significant difference was observed in cancer-specific survival after the failure of ADMT between patients with bicalutamide and those using flutamide ($P = 0.053$).

AWS was evaluated in 30 of the 48 patients for whom the second-line treatment finally had no efficacy or who had PSA failure. Only two (6.7%) had PSA decreases of 50% or more, and in three (10.0%) PSA decreased less than 50%.

Of the 48 patients, 46 received third-line treatment (Table 1). They consisted of 27 of the 28 patients who had
PSA failure after the second-line treatment and 19 of the 20 who failed to respond to the treatment. Of the 46 patients, 16 (34.8%) had a PSA response to the treatment. The median PSA failure-free survival for the 16 patients was 6.0 months. Although the estrogen group had a significantly higher response rate than the other antiandrogen group (55.0% vs. 16.0%, \( P = 0.026 \)), there was no difference in cancer-specific survival after failure of the second-line treatment between the two groups (\( P = 0.892 \)). There was no significant difference in the response rates to the third-line treatment between patients with bicalutamide as the second followed by flutamide as the third-line treatment (8.3%), and those with flutamide as the second followed by bicalutamide as the third-line treatment (11.1%, \( P > 0.99 \)).

There were 30 patients (56.6%) who died of prostate cancer. Of the 30, for 22 patients there was no efficacy and for 8 PSA failure in the third-line treatment. No patients received chemotherapy such as docetaxel in this series.

For the 53 patients who received the second- and/or third-line treatments, the 5-year survival rate from the initiation of the second-line treatment was 60.3% and the median follow-up period from the failure to the end of follow-up was 58.8 months (7.8–147.9). Cancer-specific survival in patients who responded to the second-line treatment was significantly higher than for those who did not (Fig. 1).

The risk factors for prostate cancer death after ADMT failure were analyzed. In univariate analysis, a nadir PSA of 4.0 ng/ml or greater during ADMT, duration of ADMT response shorter than 12 months and PSA-DT of less than 10 months after ADM failure were significant risk factors for death (Table 2). In multivariate analysis, a nadir PSA of 4.0 ng/ml or greater during ADMT and PSA-DT of less than 10 months after ADMT failure were independent risk factors for prostate cancer death after ADMT failure, with hazards ratios of 4.41 and 8.00, respectively. Using these risk factors, we determined how they affected the clinical courses of patients with failure of the initial ADMT. The 53 patients were divided into three groups according to the numbers of these two risk factors (Fig. 2). The 5-year cancer-specific survival rates were 100% in patients with no risk factors, 65.0% in those with one risk factor and 50.0%, and the median durations of responses were 10.7, 4.1 and 1.9 months in the three groups, respectively.

**DISCUSSION**

We retrospectively evaluated the effectiveness of the second- and third-line treatments after the failure of the initial ADMT for patients with clinical T3 or more advanced disease. Second-line treatment was effective in 62.3% of patients for a median of 10.3 months. Although there are few reports on the add-on effects of antiandrogens for patients who are initially treated with ADMT, Fuji similarly reported that the second-line treatment using bicalutamide was effective in 65.9% of 44 patients for a median of 9.2 months (8). In another report, which included patients initially treated with not only ADMT but also MAB, add-on or replacement antiandrogen treatment was effective in 22–51% of patients for a median of 6.0–8.6 months (9–11). Thus, adding antiandrogens after the failure of the initial hormonal therapy is thought to be a beneficial treatment option after both ADMT and MAB. In addition, our results suggest that there are few differences between the results obtained with different antiandrogens, as Okihara (10) and Suzuki (11) reported previously.

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Table 1. PSA responses to the third-line treatment in 46 patients

<table>
<thead>
<tr>
<th>Second-line</th>
<th>Third-line</th>
<th>Number of patients</th>
<th>Response</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide</td>
<td>Flutamide</td>
<td>12</td>
<td>1</td>
<td>8.3</td>
</tr>
<tr>
<td>EMP</td>
<td>8</td>
<td>1</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>DES-P</td>
<td>3</td>
<td>2</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>CMA</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>DXM</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>Bicalutamide</td>
<td>9</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>EMP</td>
<td>5</td>
<td>4</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>DES-P</td>
<td>3</td>
<td>3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>CMA</td>
<td>Bicalutamide</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>DES-P</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>16</td>
<td>34.8</td>
<td></td>
</tr>
</tbody>
</table>

EMP, estramustine phosphate. DES-P, diethylstilbestrol diphosphate. CMA, chlormadinone acetate; DXM, dexamethasone; PSA, prostate-specific antigen.

Figure 1. Cancer-specific survival after failure of androgen deprivation monotherapy (ADMT) in patients who responded to the second-line treatment and those who did not.
The response rate to the third-line treatment was only 34.8% in this study. Although estrogens showed the highest response rate, the duration of the response was relatively short. Since cancer-specific survival after the failure of second-line treatment was not significantly different between estrogens and antiandrogens, estrogens were not superior to antiandrogens (Fig. 3).

According to the combination of nadir PSA during ADMT and PSA-DT after the failure of ADMT, we can estimate the cancer-specific survival after the failure of the initial ADMT. These parameters were also predictors for the outcome of the second-line treatment. Thus, parameters obtained before and just after the failure of ADMT contribute to prediction of the outcome of subsequent treatment and the estimation of survival.

Recent reports have shown that docetaxel contributes to the improvement of the overall survival for patients with hormone-refractory prostate cancer (12,13). However, there is no consensus about the timing of the initiation for this chemotherapy. The most important thing to consider when treating advanced prostate cancer is minimizing adverse events due to treatment and maintaining quality of life (QOL). Thus, we should conduct well-designed prospective clinical trials to determine whether the early introduction of this chemotherapy contributes to improvement in patients with hormone-refractory disease.

In this study, we focused on patients who were initially treated with ADMT. There is controversy as to whether patients with advanced prostate cancer should be initially treated with ADMT or MAB. Recent meta-analyses have shown the superiority of initial MAB to ADMT for 5-year cancer-specific survival (3,4,14). In phase 3 trials conducted in Japan, MAB using bicalutamide was superior to ADMT in terms of not only overall survival but also the patients’ QOL, as pain and voiding dysfunction especially were improved earlier with MAB (15,16). Although we could not compare the effectiveness of initial MAB and deferred MAB in this study, initial MAB may be indicated for patients with advanced prostate cancer who have the symptoms of locally extended disease and/or metastasis.

Table 2. Univariate and multivariate Cox proportional hazards analyses for predicting cancer-specific death after failure of androgen deprivation monotherapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Univariate P-value</th>
<th>Multivariate P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8 vs. &lt;8</td>
<td>0.28</td>
<td>0.41</td>
<td>1.41 (0.62–3.23)</td>
</tr>
<tr>
<td>PSA at ADMT started (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 vs. &lt;100</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical M stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 vs. M0</td>
<td>0.14</td>
<td>0.89</td>
<td>1.06 (0.47–3.23)</td>
</tr>
<tr>
<td>Nadir PSA during ADMT (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 vs. &lt;4</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>4.41 (2.04–9.52)</td>
</tr>
<tr>
<td>Duration of ADMT response (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 vs. ≥12</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA-DT after failure of ADMT (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 vs. ≥10</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>8.00 (2.47–25.74)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; ADMT, androgen deprivation monotherapy; PSA-DT, PSA doubling time.

Figure 2. Cancer-specific survival after failure of ADMT in patients divided into three groups according to the number of risk factors.

Figure 3. Cancer-specific survival after failure of the second-line treatment in patients who used estrogens and antiandrogens for the third-line treatment.
CONCLUSIONS

In this study, the response rates to the second- and third-line treatments were 62.3% and 34.8%, respectively. Nadir PSA of 4.0 ng/ml or greater during ADMT and PSA-DT of less than 10 months after the failure of ADMT are factors to predict cancer prognosis after the failure of initial ADM.

Conflict of interest statement

None declared.

References