The Primary Local Stage at Diagnosis Predicts Regional Symptoms Caused by Local Progression in Patients With Castration-resistant Prostate Cancer

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OBJECTIVE To identify the characteristics that predict occurrence of local progression-related events (LPREs) in patients with castration-resistant prostate cancer (CRPC) to adjust its management.

METHODS We retrospectively reviewed the medical records of 39 patients with CRPC. LPREs were defined as regional symptoms caused by local progression and categorized into urinary events and rectal events. Urinary events were defined as ureteral obstruction, acute urinary retention, or hematuria requiring treatment, and rectal events were rectal obstruction or rectal bleeding caused by tumor invasion.

RESULTS The median prostate-specific antigen level at diagnosis was 185 ng/mL. During the median follow-up period of 4.4 years, 10 patients (25.6%) had LPREs. Urinary events were observed in 8 patients (20.5%) and rectal events in 2 (5.1%). The proportion of T4 in patients with LPREs was higher than in those without LPREs (70.0% vs 10.3%; $P < .001$). Stage T4 at diagnosis was an independent factor to predict LPREs in multivariate analysis (hazard ratio, 8.62; $P = .004$). The 5-year cumulative incidence of LPREs in patients with stage T4 was 70.0%, whereas in those with stage ≤T3, they were 3.6% ($P < .001$).

CONCLUSION Patients with stage T4 at diagnosis are more likely to have a risk of LPREs than those with stage ≤T3. These results indicate that patients with locally advanced prostate cancer on androgen deprivation therapy need to be closely monitored for early diagnosis of CRPC and treated with the appropriate intervention for LPREs at the appropriate time. UROLOGY 85: 430–435, 2015.

Prostate cancer is the most common noncutaneous malignancy in men in developed countries.[1] Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced prostate cancer. However, in most cases, the disease progresses despite the castration level of serum testosterone and results in castration-resistant prostate cancer (CRPC).

Some patients with CRPC experience symptoms caused by local progression, including ureteral obstruction, bladder outlet obstruction, severe hematuria, and rectal obstruction.[2-4] These can lead to poor quality of life (QOL). However, local progression is commonly accompanied by life-threatening systemic progression of CRPC. We always face a dilemma as to whether aggressive intervention for local progression provides a significant clinical effect for such patients. Thus, the strategy for local progression in patients with CRPC remains to be determined because its profile is unclear. The aim of this study was to identify the characteristics that predict occurrence of local progression-related events (LPREs) in patients with CRPC to adjust its management.

METHODS

We reviewed patients with advanced prostate cancer who initially received androgen deprivation monotherapy (ADMT) or complete androgen blockade (CAB) with an antiandrogen as the first-line treatment in our institution between 1999 and 2009 and isolated 39 patients who progressed to CRPC during the follow-up period. All patients had serum prostate-specific antigen (PSA) determination (ECLusys PSA II assay; Roche Diagnostics, Tokyo, Japan) before prostate biopsy. Systematic prostate biopsy was performed using an 18-gauge needle under the guidance of transrectal ultrasound, and 6-14 biopsy cores were taken from each patient. The clinical stage was determined via digital rectal examination, transrectal ultrasound, abdominal

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Table 1. Clinical characteristics of patients

	N = 39
Median age at diagnosis (range), y	73 (51-88)
Median PSA at diagnosis (range), ng/mL	185 (10.7-8190)
Median prostate volume (range), mL	40.2 (16.3-79.8)
Gleason score on biopsy (%)	
6	2 (5.1)
7	9 (23.1)
≥8	28 (71.8)
TNM stage (%)	
T2-4N0M0	7 (17.9)
TanyN1M0	6 (15.4)
TanyN0M1	11 (28.2)
TanyN1M1	15 (38.5)
Local symptoms at diagnosis (%)	5 (12.8)
Primary ADT (%)	
Surgical castration/LHRH agonist	11 (28.2)/22 (56.4)
CAB	5 (12.8)
LHRH antagonist	1 (2.6)
Time to progression during ADT (range), mo	9.1 (0.8-79.8)

ADT, androgen deprivation therapy; CAB, complete androgen blockade; LHRH, luteinizing hormone–releasing hormone; PSA, prostate-specific antigen; TNM, tumor-nodes-metastasis.

computed tomography, chest x-ray, and bone scanning using 99mTc-methylene-diphosphonate. The stage and histologic grade were assigned using the 2009 The Union for International Cancer Control-American Joint Committee on Cancer tumor-nodes-metastasis staging system and Gleason grading system based on the criteria of the 2005 International Society of Urological Pathology consensus conference.[5]

As the first-line treatment, 34 patients were treated with ADMT, with surgical castration for 11 patients, the administration of a luteinizing hormone–releasing hormone agonist for 22 patients and a luteinizing hormone–releasing hormone antagonist for 1 patient (Table 1). Five patients were treated with CAB, with bicalutamide 80 mg daily for 2 patients, chlormadinone acetate 100 mg daily for 2 patients, and flutamide 375 mg daily for 1 patient.

As all patients had PSA progression during ADMT or CAB, second-line treatment was done using an additional antiandrogen for those who underwent ADMT and an alternative antiandrogen for those with CAB. If PSA elevation developed during CAB, the antiandrogen was terminated, and the patient was observed for antiandrogen withdrawal syndrome. Positive antiandrogen withdrawal syndrome was defined as a PSA decline of ≥50% from the PSA level at the time when the antiandrogen was discontinued. After failure of the second-line treatment for those with the second-line CAB, another alternative antiandrogen, estrogen, glucocorticoid with ADMT, or docetaxel was given as the third-line treatment. Drugs used in the second-line or later 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. LPREs were defined as regional symptoms caused by local progression and categorized into urinary events and rectal events. Urinary events were defined as ureteral obstruction (either unilateral or bilateral), acute urinary retention, or hematuria requiring treatment, and rectal events were rectal obstruction and rectal bleeding caused by tumor invasion.

Data were extracted, including the characteristics of the patients (age, clinical stage, PSA level, prostate volume, biopsy findings, treatments, and local symptoms at diagnosis of CRPC) and local progression data (LPREs, treatments, and time to LPREs). The time of PSA progression was defined as the time of the first of 3 consecutive increases in the PSA level. Survival time from the start of the first therapy to death of prostate cancer was calculated. The Fisher exact test and the Mann-Whitney *U* test were carried out to compare various clinical variables between the groups with and without LPREs. The Fine-Gray regression model was used to calculate the probability of LPREs and prostate cancer mortality.[6] Cumulative incidence curves were used in a competing risk setting, with death without LPREs for probability of LPREs or death due to other cause for prostate cancer mortality as a competing event. The proportional hazards regression model for the subdistribution of a competing risk was used to estimate the prognostic factors of LPREs based on the optimal cutoff value for each parameter. $P < .05$ was considered to be statistically significant. All statistical analyses were performed with EZR for Windows (Saitama Medical Center, Jichi Medical University, Saitama), which is a graphical user interface for R (version 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria).[7] More precisely, it is a modified version of R commander (version 1.6-3) that was designed to add statistical functions frequently used in biostatistics.

RESULTS

The characteristics of the patients are shown in Table 1. The median PSA level at diagnosis was 185 ng/mL. Stage T2 was observed in 3 patients (7.7%), T3 in 26 (66.7%), and T4 in 10 (25.6%). Although 5 patients had local symptomatic events such as ureteral obstruction and urinary retention at diagnosis, all of them improved immediately after the primary ADT (ADMT or CAB).

The profiles of all patients with LPREs are shown in Table 2. During the median follow-up period of 4.4 years, 10 patients (25.6%) had LPREs. Urinary events were observed in 8 patients (20.5%) and rectal events in 2 patients (5.1%). Of the 3 patients with ureteral obstruction, 2 patients (No. 1 and 2) underwent bilateral percutaneous nephrostomy because of suffering and renal insufficiency. Of the 4 patients with acute urinary retention, 2 patients (No. 4 and 5) were successfully treated with clean intermittent self-catheterization. One patient (No. 6) gave up self-catheterization and underwent percutaneous cystostomy because catheterization induced occasional hematuria. The other one (No. 7) with urinary retention had urinary catheter placement because of severe systemic progression of CRPC. One patient (No. 8) with severe hematuria was successfully treated with transurethral electrocoagulation (TUEC). Of the 2 patients with rectal bleeding and obstruction, 1 patient (No. 9) underwent colostomy and cystostomy, and the other (No. 10) was observed because of severe systemic progression. Median survival after LPREs was 2.4 years.

We compared the characteristics of patients with LPREs and those without them. The proportion of T4 in patients with LPREs was higher than in those without