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Comparison of chronological changes in urinary function in patients who underwent low-dose-rate brachytherapy for prostate cancer—A randomized controlled trial of alpha-1 adrenoceptor antagonist alone versus combination with cyclooxygenase-2 inhibitor—

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ABSTRACT

PURPOSE: To evaluate the add-on efficacy of a cyclooxygenase (COX)-2 inhibitor on the chronological changes in urinary function in patients who underwent low-dose-rate prostate brachytherapy.

METHODS AND MATERIALS: A total of 310 patients with prostate cancer who underwent low-dose-rate-brachytherapy were enrolled. Patients were randomized and allocated to the monotherapy group (tamsulosin alone: 0.2 mg/d) and the combination group (tamsulosin 0.2 mg/d plus celecoxib: 200 mg/d). We compared the chronological change in the international prostate symptom score (IPSS), the overactive bladder symptom score (OABSS), uroflowmetric parameters, and the frequency volume chart.

RESULTS: There was not a significant difference between the two groups in the chronological changes in IPSS and OABSS for 12 months after implantation. Regarding the frequency volume chart assessment, the mean daytime urinary frequency in the combination group at 3 and 6 months after implantation was significantly lower than that in the monotherapy group. Regarding IPSS recovery at 3 months after implantation, higher baseline IPSS and nonuse of external beam radiation therapy were independent factors, while smaller prostate volume and higher baseline IPSS were independent factors of IPSS recovery at 12 months after implantation based on multivariate analyses.

CONCLUSIONS: There was not an additional effect of a COX-2 inhibitor to the action of an alpha-1 adrenoceptor antagonist on concerning the chronological changes in IPSS and OABSS. The use of a COX-2 inhibitor reduced the daytime urinary frequency and postvoid residual after seed implantation.

Keywords: Prostate cancer; Brachytherapy; COX-2 inhibitor; Urinary morbidity; Frequency volume chart; Randomized controlled trial

Introduction

Low-dose-rate (LDR) brachytherapy is widely used for patients with prostate cancer because of its excellent oncologic outcome, similar to that of radical prostatectomy and intensity-modulated radiation therapy (1–5). More than 50% of patients suffer from urinary frequency and urgency for 6 months after seed implantation, and this is a problem that remains to be solved (6–8). An alpha-1 adrenoceptor antagonist is usually used to prevent and relieve these symptoms. However, the efficacy of alpha-1 adrenoceptor

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antagonists on these adverse events has inevitably been concluded to be inadequate and limited based on previous studies (6,9–11).

If urinary frequency and urgency are caused by inflammation due to mechanical stimulation by needle insertion and seed implantation or a radiation effect, anti-inflammatory agents should be effective to solve these adverse events. Crook *et al.* reported the pretreatment effect of a cyclooxygenase (COX)-2 inhibitor in patients who underwent LDR brachytherapy (12). However, the prophylactic efficacy has not been evaluated before. Under these circumstances, we projected a randomized controlled trial (UMIN000003649) to evaluate the add-on efficacy of a COX-2 inhibitor on chronological changes in lower urinary tract symptoms and function after LDR brachytherapy.

Methods and materials

A total of 360 patients who were clinically diagnosed with prostate cancer (cT1c-3aN0M0) underwent LDR brachytherapy at Nara Medical University Hospital between May 2010 and July 2013. Of them, 310 patients who provided written informed consent were enrolled in this randomized controlled trial. Patients were allocated to one of two treatment groups (tamsulosin alone: 0.2 mg/d vs. tamsulosin: 0.2 mg/d plus celecoxib: 200 mg/d) by irradiation modality (seed implantation alone vs. combination with external beam radiation therapy [EBRT]), neoadjuvant androgen deprivation therapy (ADT), and pretreatment international prostate symptom score (IPSS) as an adjustment factor. Medication with tamsulosin was continued for at least 6 months after seed implantation or until the IPSS returned to the pretreatment score or less, while celecoxib was continued for 3 months. The maximum approved dosage of tamsulosin is 0.2 mg in Japan.

The prescribed dose of seed implantation alone was 160 Gy, whereas that of combination with EBRT was 110 Gy. The target portion of EBRT was determined 1 month after seed implantation, and the patients received 45 Gy (in 25 fractions of 1.8 Gy per fraction) using 10-MV photon energy and three-dimensional conformal technique. The clinical target volume included both the entire prostate and the proximal third of the seminal vesicles.

The primary endpoint was the change in IPSS at 3 months after seed implantation. The secondary endpoints were the effects of chronological changes in IPSS, overactive bladder symptom score (OABSS), maximum flow rate, voided volume per micturition and postvoid residual (PVR) on uroflowmetry, urinary frequency, total and mean voided volume on a 48-h frequency volume chart (FVC), and the recovery rate of IPSS at 12 months after seed implantation. Each score was evaluated before seed implantation and at 1, 3, 6, and 12 months later. Recovery at 3 and 12 months after was defined as a return of the IPSS to the pretreatment score or less.

The baseline characteristics between the two groups were tested by the χ^2 test for categorical variables and a *t*-test for continuous variables. The chronological change in each parameter was tested between the pretreatment score and each measured period by a paired *t* test. The difference in inter-group comparison was tested by a *t* test. Sample size calculations indicated that 62 patients in each group would be needed to detect at least a 25% difference in efficacy between the two study groups with α equal to 0.05 and power equal to 80%.

We conducted both univariate and multivariate logistic regression analyses (stepwise selection method) using clinical parameters (age, neoadjuvant ADT, combination of EBRT, prostate volume at postdosimetry, IPSS at baseline, IPSS quality of life score at baseline, OABSS at baseline, randomized arms [tamsulosin alone vs. tamsulosin plus celecoxib]), and postoperative postimplant dosimetric parameters to elucidate the predictive parameters of IPSS recovery to the baseline level at 3 and 12 months after seed implantation. The postimplant dosimetric parameters analyzed in this study were minimal percentage of the dose and minimal dose (Gy) received by 90% of the prostate gland (%D_{90}/D_{90}), the percentage of the prostate volume receiving 100% and 150% of the prescribed minimal peripheral dose ($V_{100/150}$), the minimal percentage of the dose and minimal dose (Gy) received by 5% of the urethra (%UD_5/UD_5), the minimal percentage of the dose and minimal dose (Gy) received by 30% of the urethra (%UD30/UD30), the minimal percentage of the dose and minimal dose (Gy) received by 90% of the urethra (%UD_{90}/UD_{90}), and the rectal volume (mL) receiving 100% of the prescribed dose (R100). Postimplant CT scanning and postimplant dosimetric studies were performed by the same radiation oncologist (AI) at 1 month after seed implantation. The parameters that showed univariate significance (*p*-value of less than 0.05) were input into multivariate models.

All statistical analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL). All *p*-values of less than 0.05 were considered statistically significant. This study was performed in compliance with the Helsinki Declaration. The institutional review board approved this prospective study, and informed consent was obtained from all patients after explaining the aim and methods of this study.

Results

Tamsulosin plus celecoxib were administered to 154 patients (combination group), and tamsulosin alone was administered to 156 patients (monotherapy group). No patient stopped the medication due to adverse events of celecoxib. And no patient of the monotherapy group received celecoxib administration due to urinary disorders.

Sixty-nine patients (45%) in the combination group and 64 patients (41%) in the monotherapy group, respectively, received neoadjuvant ADT. No patients received