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Feasibility of enzalutamide on patients with recurrent non-muscle-invasive bladder cancer with marker tumors: phase I study

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Abstract

Objective Recent preclinical and retrospective clinical evidence shows that androgen receptor (AR)-mediated signals have significant roles in development of non-muscle invasive bladder cancer (NMIBC). Here, we conducted a single-center, phase I study to assess the feasibility and efficacy of enzalutamide in patients having recurrent NMIBC with marker tumors. Patients with NMIBC who cannot achieve complete transurethral resection (TUR) or with recurrence within a year after the TUR, were enrolled. The patients were administered oral enzalutamide at 160 mg dose, once daily for four weeks. Clinical response at the end of the treatment was evaluated using cystoscopy.

Results Of the six patients enrolled, two experienced multiple recurrences. All the patients received the planned administration of enzalutamide. Enzalutamide was tolerable and all patients were able to complete the planed treatment, although four patients experienced mild treatment-related adverse events (AEs), but AEs with grade 2 or more were not observed. As for efficacy, three patients showed no change while the remaining three showed disease progression. Immunohistochemical analysis did not showed the strong staining of AR in the latest tumors. This is the first clinical study on enzalutamide treatment for NMIBC patients. In this study, four weeks of enzalutamide administration was well tolerated, however showed no clinical response for non-strong staining of AR.

Trial registration: University Hospital Medical Information Network UMIN000026520 (date registration: 2017/3/13).

Keywords Non-muscle invasive bladder cancer, Enzalutamide, Androgen receptor, Phase 1 study

Introduction

Bladder cancer (BC) is the fourth most common malignancy in men, the 12th most common in women [1], and non-muscle-invasive bladder cancer (NMIBC) is detected at the initial diagnosis in ~ 80% of these patients. Furthermore, ~ 50% of NMIBC patients show recurrence despite current intravesical instillation therapy with anti-cancer drugs or Bacillus Calmette-Guérin (BCG); ~ 10% eventually progress to muscle-invasive BC [2]. Epidemiological studies have shown that men have an approximately three times higher risk of developing BC than women and recent reports revealed that sex hormones and their receptor signals play an important role in BC carcinogenesis [3–7]. Among these studies, several preclinical models have revealed the involvement of androgen receptor (AR) signaling in BC development

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[3, 8, 9]. Moreover, recent retrospective clinical studies suggested that androgen deprivation therapy for prostate cancer prevents bladder cancer development [10] and recurrence [11]. The AR expression was significantly higher in non-muscle-invasive tumors (51–75%) compared to muscle-invasive tumors (21–33%) [12]. The AR is expected to be a potential therapeutic target for BC.

Enzalutamide is a synthetic AR signaling inhibitor that blocks androgen binding to the AR and also prevents nuclear translocation, binds DNA, and co-activator recruitment of AR in prostate cancer cells [13–15]. Recently, enzalutamide was shown to inhibit tumorigenesis in an AR-positive urothelial cancer cell line using a mouse xenograft model [7, 16]. Another report showed that enzalutamide efficiently inhibited the proliferation of AR-positive urothelial cancer cell-lines by inducing apoptosis [17]. However, before Phase II trials, dosage, safety (with regard to adverse events [AEs]), and non-AR-related effects on NMIBC tumors must be determined to fully evaluate the parameters for Phase II trials.

Based on previous observations, we surveilled the AEs and effects of enzalutamide on a small cohort of NMIBC patients at the standard dosage in a Phase I trial designed to facilitate a subsequent Phase II trial [18]. In this our single-center, single-arm, prospective phase I study, we aimed to test the feasibility and efficacy of enzalutamide in NMIBC patients with marker tumors.

Main text

Study design and treatment plan

This was a single-arm, single-center, prospective phase I study to investigate the safety of enzalutamide in NMIBC patients as well as record tumor effects related with AR-expression. Patients received oral enzalutamide at the standard dose of 160 mg/daily for four weeks. The primary endpoint was tumor response and the secondary endpoints were adverse events. The study planned to enroll 10 patients total, but if no serious safety concerns or serious tumor-related effects were observed in the initial six patients, the study was to be concluded. The protocol was approved by the Internal Review Board of the Tsukuba University Hospital (approval number: H28-260). Patients provided written, informed consent that included the right to opt out at any time, and this trial was registered at the University hospital Medical Information Network Clinical Trials Registry (UMIN000026520). Frequency and procedures for auditing trial conduct was done annually, and the process was independent from investigators. We used the SPIRIT reporting guidelines [19].

Patient population

Eligibility criteria included male patients with histologically confirmed NMIBC; evaluable tumor lesions [after incomplete transurethral resection of the bladder tumor (TURBT) or recurrence of tumor within 1 year after the last treatment]. Patients were required to have a performance status less than one and adequate organ function (granulocyte count > 2000/mm^3, platelet count > 100,000/mm^3, hemoglobin > 8.0 g/dL, serum creatinine < 1.5 mg/dL, AST < 100 IU/L, and ALT < 100 IU/L). Exclusion criteria included history of medications affecting testosterone for benign prostatic hyperplasia or prostate cancer and history of intravesical therapy after the last TURBT.

Study evaluations

Patients were evaluated before enzalutamide administration. This included evaluation of vital signs, biochemical and hematological laboratory testing, cystoscopy, and history of medication. Patients visited the hospital two or four weeks after the initiation of the enzalutamide administration. Patients who visited two weeks after initiation underwent evaluation of AEs, including interview, vital signs, and laboratory testing. Those who visited four weeks after underwent cystoscopy in addition to the above AE evaluations. In pre- and post-treatment cystoscopy, the sizes of all visible tumors were measured using forceps and calipers. The tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST): version 1.1. Although, in general, the RECIST is not definitive with regard to manual measurement, it served as a baseline for indicating any changes in tumor status due to the study drug. In the present study, small lesions with the longest diameter (3–6 mm), were also included in the target lesion, if the lesion could be measured accurately.

Enzalutamide has been proven to interact with the AR, but off-target effects must be evaluated before the Phase II trials. Thus, AR expression for all tumors was conducted immunohistochemically. The formalin-fixed section (4 μm thick) of the last TURBT specimens (before enzalutamide treatment) were stained with primary antibody to AR clone AR441 (dilution 1:100; Carpinteria, CA, USA). As a positive control, the prostate tissue was included to assure proper staining. If patients underwent TURBT after enzalutamide treatment, the resected tumors were also evaluated for AR expression.

Results

A total of six patients with recurrent BC were enrolled and treated with enzalutamide (between April 2017 and March 2018). Patient characteristics are detailed in

Table 1 Background of patients

Case	Age	Prior recurrence	Patholoy of the latest tumor before enzalutamide			Time to the last recurrence	Existing Tumors at enzalutamide administration	
			Stage	Grade	AR expression		Number	Lagest size
1	69	None	T1	G2	No	1 Month	1 Tumor	6 mm
2	68	1 Time	T1	G3	No	1 Month	1 Tumor	3 mm
3	67	2 Times	Ta with CIS	G3	No	4 Months	1 Tumor	5 mm
4	66	None	T1	G3	No	1 Month	1 Tumor	3 mm
5	57	None	Ta	G2	No	8 Months	4 Tumors	5 mm
6	52	None	T1	G3	No	1 Month	1 Tumor	4 mm

Table 1. One patient experienced two prior recurrences and another experienced one prior recurrence before the last recurrence. The remaining four patients had no prior recurrences. The pT stages of the latest tumors were Ta (one patient); Ta with concomitant carcinoma-*in-situ* (CIS) (one patient); and T1 (four patients) with pathological grades: G1(0), G2(2) and G3(4), respectively. Immunohistochemically, no tumor revealed AR staining, confirming that all drug-related effects were non-AR-related. The median time until the last recurrence was three months with one month as the shortest interval. The number of existing tumors at enzalutamide administration was between one and four, with the largest measuring 6 mm.

All six patients were administered the planned 4-week enzalutamide regimen. During treatment, four of them experienced at least one AE, including fatigue, diarrhea, constipation, and impaired concentration. However, all the AEs were Grade 1 and Grade 2 or higher events were not observed. Laboratory tests revealed no abnormal findings. All the AEs were managed without administration of drugs and were resolved within a month.

Table 2 summarizes the response and treatment outcome after enzalutamide treatment. Three patients were defined to have progressive disease (PD) because of tumor enlargement (two patients) and appearance of a new lesion (one patient). The remaining three were defined to have stable diseases (SD). Per study protocol, the trial was closed early because no objective tumor response or unexpected AEs were observed in the initial six patients.

All six patients underwent TURBT after the completion of enzalutamide and subsequent complete resection of tumors. Pathological diagnoses were Ta (two patients); Ta with concomitant CIS (two patients); Tis (one patient); T1 (one patient); and atypical urothelium (one patient). Immunohistochemical expression of AR was not detected in any of the tumors. Five patients received adjuvant intravesical treatments. However, two patients experienced further recurrence, of whom one underwent total cystectomy but ultimately died of the cancer.

Discussion

In the present prospective study, all the patients received the planned administration of enzalutamide. Enzalutamide was tolerable and all patients were able to complete the planed treatment. Although four patients experienced mild treatment-related AEs, AEs with grade 2 or more were not observed. However, no objective response was observed in the six patients after four weeks of enzalutamide administration.

This study protocol required at least one objective response during treatment for the initial six patients. Although enzalutamide was tolerated by this patient group, this trial was closed earlier because no objective response was observed in the initial six patients per study protocol.

There are several explanations for the insufficient efficacy noted here. First, the adequate treatment period is largely unknown, and four weeks of administration might have been inadequate for NMIBC patients treated with enzalutamide. We planned this schedule by referring to the results of the clinical study on enzalutamide monotherapy in hormone-naïve prostate cancer, where a favorable prostate specific antigen response was observed during the first 5 weeks [20]. Patients with NMIBC might have a different response pattern to enzalutamide. However, this was considered appropriate, and a safety treatment plan was made because three out of the six patients showed PD after four weeks of treatment.

Second, more importantly, immunohistochemical expression of AR was not detected in all the examined tumors. This was an unexpected result. Although evidences of immunohistochemical expression of AR are available, its positive rate in NMIBC highly varies between 9.0 to 75.0% [21]. Despite differences in staining methodology, the positive rate was known to depend

Table 2 Response and outcome after enzalutamide administration

Case	Tumor size	New lesions	Response	Patholoy of the resected tumor after enzalutamide				Clinical course after enzalutamide administration		
				Stage	Grade	AR expression	EAU score	Recurrenc e	Treatment	Outcomes
1	33% increased	no	PD	Ta	G2	No	3	None	BCG*	No evidence of disease (25Ms)
2	67% increased	yes	PD	Ta with CIS	G2	No	7	2 Times	BCG*	Alive with disease (26Ms)
3	0% increase	No	SD	Ta with CIS	G3	No	5	1 Time	MMC*, total cystectomy	Dead of disease (16Ms)
4	0% increase	No	SD	Atypical urotheliuml	–	No	–	None	BCG*	No evidence of disease (18Ms)
5	64% increased	No	PD	Ta	G1	No	5	None	no	No evidence of disease (17Ms)
6	0% increase	No	SD	Tis	G2	No	4	None	BCG*	No evidence of disease (16Ms)

*Intravesical instillation

on clinicopathological features of the examined tumors. Although previous studies have shown that a high AR expression was associated with low grade tumor and low risk of recurrence [22, 23], some studies have reported conflicting results [12, 24]. The recently published meta-analysis of immunohistochemical studies demonstrated that AR positivity was significantly associated with low-grade tumors and showed better recurrence free survival [25]. Chemoprevention is one of the future directions of AR-targeted therapy for BC. As the participants of the present study were recurrent NMIBC patients, AR-targeted therapy could not be effective in this setting. Furthermore, as shown in Table 2, most of the enrolled patents had high-grade tumor and high-risk clinicopathological features for recurrence with a median EAU score of 5 (3–7). Therefore, the unfavorable features resulted in an unexpectedly low positive rate of AR expression in the present study.

There was a phase II clinical trial conducted to test the chemo-preventive effect of enzalutamide in NMIBC (NCT02605863). Unfortunately, the trial was terminated early because of low enrollment. In this study, similar to the present study, AR expression of tumor was not included in the eligibility criteria. Based on the results presented here, we strongly recommend that AR expression status should be included in the eligibility criteria in a clinical trial of BC. Recently, a phase II study of enzalutamide, gemcitabine and cisplatin in metastatic BC was completed [20], in which, AR expression in tumor tissues and circulating tumor cells were tested.

In conclusion, four weeks of enzalutamide administration was well tolerated, however no clinical response was observed in patients with negative AR-staining NMIBC. Results from this first report showed enzalutamide to be ineffective in NMIBC patients after incomplete resection or early recurrence. When considering the enzalutamide administration for NMIBC, the AR-staining should be included in eligibility criteria, and treatment duration is needed for more than four weeks for future clinical trials.

Limitations

In this study, a phase I trial was conducted to investigate the safety of enzalutamide in NMIBC patients as well as to evaluate tumor effects regardless of AR staining. Although unexpected AEs were observed in the initial six patients, no objective tumor response was observed. Immunohistochemical staining revealed no AR staining in any tumors, confirming that all drug-related effects were non-AR-related. Consequently, enzalutamide did not demonstrated effectiveness in AR-negative NIMBC patients, suggesting that targeted treatment for AR-positive NMIBC patients is necessary.

Abbreviations

AE	Adverse event
AR	Androgen receptor
BCG	Bacillus Calmette-Guérin
BC	Bladder cancer
CIS	Carcinoma-in-situ
NMIBC	Non-muscle invasive bladder cancer
PD	Progressive disease
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable diseases
TUR	Transurethral resection
TURBT	Transurethral resection of the bladder tumor

Supplementary Information

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Supplementary Material 1: SPIRIT check list.

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Author contributions

T,Ka., S,K. and H,N. designed and directed the project. T,Ka., T,Ko. and S,M. analyzed and interpreted the patient data. T,Ka. and M.B wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Internal Review Board of the Tsukuba University Hospital (approval number: H28-260). Patients provided written, informed consent that included the right to opt out at any time. This trial was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000026520).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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