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ORIGINAL ARTICLE

The impact of genetic polymorphism on *CYP19A1* in androgen-deprivation therapy among Japanese men

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Abstract

Purpose Inadequate suppression of testosterone during androgen-deprivation therapy impairs its efficacy. This study investigated the significance of genetic polymorphism in *CYP19A1*, which encodes aromatase that catalyzes androgens into estrogens, among men treated with primary ADT for metastatic prostate cancer.

Methods This study included 80 Japanese patients with metastatic prostate cancer whose serum testosterone levels during ADT were available. The association of *CYP19A1* gene polymorphism (rs1870050) with clinicopathological parameters including serum testosterone levels during ADT as well as progression-free survival and overall survival was examined.

Results Serum testosterone levels during ADT of men carrying homozygous wild-type (AA) in the *CYP19A1* gene [median (interquartile range); 11.6 (8.3–20.3) ng/dl] were higher than those in men carrying the heterozygous/homozygous variant (AC/CC) [median (interquartile range); 10.0 (6.4–12.8) ng/dl]. When adjusted by Gleason score, initial PSA, M-stage and serum testosterone level during ADT, heterozygous/homozygous variant (AC/CC) in the *CYP19A1* gene was associated with a lower risk of progression to castration resistance [hazard ratio (95% confidence interval), 0.53 [0.29–0.92], $p=0.025$], but not to any-cause death [hazard ratio (95% confidence interval), 0.74 [0.36–1.49], $p=0.40$].

Conclusions These findings suggest that genetic variation in *CYP19A1* (rs1870050) might affect the prognosis of patients with metastatic prostate cancer when treated with ADT by regulating serum testosterone levels.

Keywords Androgen-deprivation therapy · Aromatase · *CYP19A1* · Prostate cancer · Testosterone

Introduction

Androgen-deprivation therapy (ADT) is the standard therapy for metastatic prostate cancer [1]. Although ADT is usually effective for prostate cancer at the initial stage, most prostate cancer patients administered ADT develop castration-resistant prostate cancer (CRPC) under hypophysiological serum testosterone levels, where persistent androgens are active despite ADT, leading to progression to CRPC. Serum testosterone level during ADT is a prognostic biomarker in primary ADT [2, 3]. To date, a small number of factors have been reported to affect serum testosterone level during ADT including age [4] and genetic polymorphisms in *SRD5A2* [3] and *GNRH2* [5].

Androgens including testosterone are metabolized by various enzymes such as 17α-hydroxylase, 17,20-lyase, 3β-hydroxysteroid dehydrogenase, aldo–keto reductase, and 5α-reductase [6]. In addition, aromatase encoded by *CYP19A1* catalyzes androstenedione and testosterone into estrone (E1) and estradiol (E2), respectively [7]. Aromatase is expressed mainly in the gonads and in peripheral sites including the prostate gland [8]. In addition, aromatase expression and activity are influenced by hormonal and nutritional factors [9], and can be affected by inherited

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genetic variants, leading to changes in sex hormone levels in the serum. Indeed, genetic polymorphisms in the *CYP19A1* gene were associated with sex hormone level including testosterone in serum among men with or without prostate cancer [10, 11]. To date, several studies have reported an association between genetic polymorphisms in *CYP19A1* and prognosis during ADT [7, 11–13]. Ross et al. identified a genetic variant in *CYP19A1* (rs1870050), located in the first exon (5′-UTR) close to the major promoter in the placenta (promoter I.1) [14], as a prognostic marker of progression risk in ADT among 129 polymorphisms across 20 genes involved in androgen metabolism [13]. However, the opposite prognostic impact of a genetic variant in *CYP19A1* (rs1870050) was reported between Caucasian and Asian populations [7].

Thus, although the genetic variant in *CYP19A1* (rs1870050) was suggested to be prognostic in ADT, its impact remains controversial among different populations. In addition, no study has reported an association between serum testosterone level during ADT and genetic variant in *CYP19A1*. Therefore, this study explored the significance of genetic polymorphism in *CYP19A1* (rs1870050) on serum testosterone levels during ADT and prognosis in Japanese men with metastatic prostate cancer treated with primary ADT.

Materials and methods

Japanese patients treated with primary ADT for metastatic prostate cancer at the University of Occupational and Environmental Health (Kitakyushu, Japan) and Kyushu University Hospital (Fukuoka, Japan) between 1993 and 2005 were included as previously described [5]. Only patients whose serum testosterone levels during ADT were available were included. Written informed consent was obtained from all patients. This study was approved by each institutional review board. Genotyping of *CYP19A1* (rs1870050) was performed as previously described [15, 16]. Briefly, genotyping using genomic DNA extracted from patient whole blood samples was performed on a CFX Connect Real-Time System (Bio-Rad, Hercules, CA, USA) with pre-designed TaqMan SNP Genotyping Assays (Life Technologies, Carlsbad, CA, USA) for rs1870050 (C__11672268_20) in *CYP19A1* and TaqMan Gene Expression Master Mix (Life Technologies), according to the manufacturer's protocol.

Serum testosterone levels were measured by an electrochemiluminescence immunoassay using patient blood obtained between 8:00 A.M. and 10:00 A.M. Serum testosterone levels during ADT were measured several times (median 2 times; range 1–5 times) on the basis of the physician's judgment, and the mean serum testosterone value during ADT was used as a representative value [3]. The data on serum testosterone level were collected before performing genotyping. Clinical TNM staging was determined in accordance with the unified TNM criteria based on the results of digital rectal examination, transrectal ultrasound, magnetic resonance imaging, computed tomography, and bone scan [17]. ADT was performed with surgical castration or continuous medical castration using a GNRH agonist (goserelin acetate or leuprorelin acetate) and/or an antiandrogen agent (bicalutamide, flutamide, or chlormadinone acetate). Progressive disease was defined as an increase in serum prostate-specific antigen (PSA) levels of >2 ng/mL and a 25% increase over the nadir, the appearance of a new lesion, or the progression of one or more known lesions classified according to the Response Evaluation Criteria in Solid Tumors [18].

All statistical analyses were performed using JMP11 software (SAS Institute, Cary, NC, USA). Categorical and continuous data were analyzed by Pearson's chi square and Wilcoxon rank sum tests, respectively. Univariate and multivariate analyses were performed using the Cox hazard proportional model to estimate hazard ratios (HRs). All p values are two-sided. p values <0.05 were considered significant.

Results

The relationship between genetic variation in CYP19A1 and serum testosterone levels during ADT

The clinical and pathological characteristics of 80 Japanese patients with metastatic prostate cancer are shown in Table 1. Genotyping revealed the distribution of homozygous wild-type (AA), heterozygous variant (AC), and homozygous variant (CC) to be 52 (65.0%), 21 (26.3%), and 7 (8.8%) men, respectively. Patient characteristics were comparable between patients who were homozygous wild-type (AA) or heterozygous/homozygous variant (AC/CC) (Table 1). The association between genetic polymorphism in *CYP19A1* and serum testosterone levels during primary ADT was analyzed and showed serum testosterone levels during primary ADT were higher in men with homozygous wild-type (AA) [median (interquartile range, IQR); 11.6 (8.3–20.3) ng/dl] than those with the heterozygous/homozygous variant (AC/CC) [median (IQR); 10.0 (6.4–12.8) ng/dl] (Fig. 1). There is no difference in serum testosterone levels during ADT between the heterozygous variant (AC) and homozygous variant (CC) (data not shown). Because age affects serum testosterone levels during ADT [4], adjustment for age was performed and demonstrated that homozygous wild-type (AA) was still associated with high serum testosterone levels during ADT ($p=0.045$). In addition, the association between

Table 1 Clinicopathological characteristics among patients who underwent primary androgen-deprivation therapy according to *CYP19A1* polymorphism (rs1870050)

Variable	All ($n=80$)	*CYP19A1* (rs1870050)		p value
		AA ($n=52$)	AC/CC ($n=28$)	
Median age, years (IQR)	72 (66–74)	71 (66–74)	72 (65–75)	0.89
Median PSA level at diagnosis, ng/ml (IQR)	223.0 (78.2–1016.7)	223.0 (78.5–1168.7)	229.1 (52.8–893.5)	0.63
Biopsy Gleason score, *n* (%)				
7	24 (33.8%)	16 (36.4%)	8 (29.6%)	
>7	47 (66.2%)	28 (63.6%)	19 (70.4%)	0.56
NA	9	8	1	
Clinical T-stage, *n* (%)				
cT2/3	52 (74.3%)	37 (77.1%)	15 (68.2%)	
cT4	18 (25.7%)	11 (22.9%)	7 (31.8%)	0.43
NA	10	4	6	
Clinical N-stage, *n* (%)				
N0	29 (40.8%)	20 (41.7%)	9 (39.1%)	
N1	42 (59.2%)	28 (58.3%)	14 (60.9%)	0.84
NA	9	4	5	
Clinical M-stage, *n* (%)				
M0	8 (10.0%)	6 (11.5%)	2 (7.1%)	
M1	72 (90.0%)	46 (88.5%)	26 (92.9%)	0.53
Hormonal therapy				
Combined androgen blockade	72 (90.0%)	47 (90.4%)	25 (89.3%)	
Castration	8 (10.0%)	5 (9.6%)	3 (10.7%)	0.88

IQR interquartile range, *NA* not available, *PSA* prostate-specific antigen

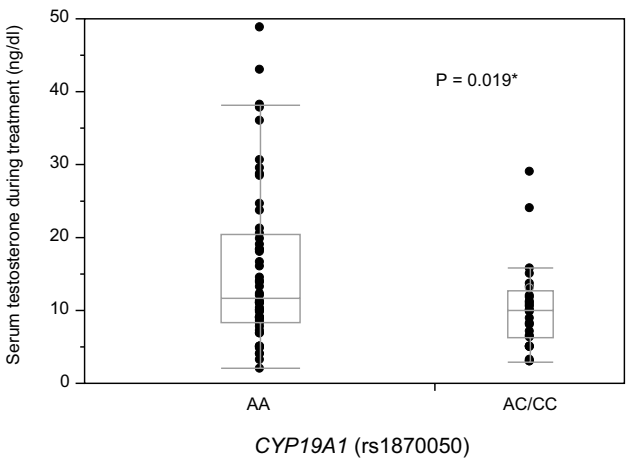

Fig. 1 Serum testosterone levels during ADT stratified by genetic polymorphism (rs1870050) in *CYP19A1* (AA vs AC/CC)

genetic variation in *CYP19A1* and serum testosterone levels was still significant when adjusted by genetic polymorphisms in *SRD5A2* and *GNRH2* (data not shown), which were shown to be associated with serum testosterone levels [3, 5].

The impact of genetic variation in CYP19A1 on the prognosis of primary ADT

Next, we analyzed the prognostic impact of genetic polymorphism in *CYP19A1* on progression-free survival (PFS) and overall survival (OS). During a median follow-up of 3.8 (IQR 1.8–7.9) years, progression and any-cause death occurred in 66 men (82.5%) and 44 men (55.0%), respectively. On univariate analyses, genetic variation in *CYP19A1* (homozygous wild-type vs. heterozygous/homozygous variant) was not associated with PFS and OS (Table 2). On multivariate analyses incorporating Gleason score, initial PSA, M-stage, and serum testosterone level during ADT as parameters, the risk of progression among men with heterozygous/homozygous variant (AC/CC) in *CYP19A1* (rs1870050) was lower compared with men with homozygous wild-type (AA) (HR; [95% confidence interval], 0.53 [0.29–0.92], $p=0.025$) (Table 2). However, there was no significant difference in OS between homozygous wild-type (AA) and heterozygous/homozygous variant (AC/CC) (HR; [95% confidence interval] 0.74 [0.36–1.49], $p=0.40$) (Table 2). As well, there is no difference in PFS and OS between the heterozygous variant (AC) and homozygous variant (CC) (data not shown).

Table 2 Prognosis stratified by *CYP19A1* polymorphism (rs1870050)

Alleles	Progression-free survival		Overall survival		Progression-free survival		Overall survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Adjusted HR[†] (95% CI)	*p* value	Adjusted HR[†] (95% CI)	*p* value
AA (*n* = 52)	Ref		Ref		Ref		Ref	
AC/CC (*n* = 28)	0.72 (0.42–1.19)	0.21	0.91 (0.47–1.69)	0.77	0.53 (0.29–0.92)	0.025*	0.74 (0.36–1.49)	0.40

HR hazard ratio, *CI* confidence interval

*Statistically significant

[†]Adjusted by Gleason score, initial PSA, M-stage, and serum testosterone level during ADT

Discussion

The sufficient suppression of androgens during ADT is critical to obtain a favorable therapeutic effect with ADT [2, 3]. This is supported by recent studies showing that CYP17 inhibitor abiraterone acetate markedly reduced androgen levels and provided survival benefit in men with metastatic hormone-sensitive prostate cancer [19, 20]. Previously, genetic variations in genes involved in the androgen-producing pathway including *SRD5A2* (rs523349) and *GNRH2* (rs6051545) were reported to be associated with serum testosterone levels during ADT and the prognosis of ADT [3, 5, 21]. Similarly, the current study investigated the impact of a genetic polymorphism in *CYP19A1* on serum testosterone levels during ADT and prognosis. We found different serum testosterone levels during ADT dependent upon genetic variation (rs1870050) in *CYP19A1*, where serum testosterone levels were lower in men carrying the variant allele, which might induce higher aromatase activity. Previously, it was reported that single-nucleotide polymorphisms (SNPs) in the *CYP19A1* gene were associated with sex hormone levels including testosterone in the serum [10, 11] although an analysis of rs1870050 was not included. To date, data on serum androgen levels including testosterone during ADT have not been reported. Although the mechanism of how the genetic variation (rs1870050) in *CYP19A1* affects the activity of aromatase remains unclear, it may influence *CYP19A1* gene expression because rs1870050 is located in the 5′-UTR region close to the functional promoter of the *CYP19A1* gene. However, further investigation of the biological mechanism as well as validation studies on the association with serum androgen levels during ADT in other ethnicities is required.

Several studies have reported a relationship between genetic variation in *CYP19A1* and risk of prostate cancer, but with inconsistent findings [7]. Furthermore, genome-wide association studies have failed to indicate a significant association between polymorphisms in the *CYP19A1* gene and prostate cancer susceptibility. Consistent with the result of testosterone level in serum, the current study identified a significantly lower risk of progression to castration-resistant prostate cancer among men carrying variant allele in *CYP19A1* gene (rs1870050) when treated with primary ADT for metastatic prostate cancer. In contrast, previous study has shown a higher risk of progression during ADT among residents in North America with the variant allele [13]. However, Lévesque et al. reported progression risk was lower among Taiwanese with the variant allele during ADT suggesting the opposite impact of the SNP in the *CYP19A1* gene (rs1870050) on progression risk during ADT. Differences in the outcome between populations may be related to different haplotypes tagged by the SNP (rs1870050) and allele frequency in different ethnic groups. To date, [TTTA] repeats [12] and SNP (rs4775936) [11] in the *CYP19A1* gene were reported to be associated with survival in a Japanese cohort treated with ADT. These data support the idea that haplotypes tagged by SNP may affect survival among men treated with ADT.

Theoretically, aromatase inhibition impairs the suppressive effect of ADT for prostate cancer by increasing the concentration of androgens. Indeed, a worse prognosis was reported for radical prostatectomy patients with a lower expression of aromatase in tumors and stroma [22]. Furthermore, several clinical trials for advanced prostate cancer and CRPC failed to show promising therapeutic effects of aromatase inhibitors [23–25], consistent with in vitro experimental data [26].

This study had several limitations including its retrospective design and relatively small sample size which may result in a reduced statistical power. In addition, the timing and frequency of serum testosterone measurements differed between cases, which may affect the data on serum testosterone levels as well as the association with the prognosis in ADT. Moreover, this study did not examine androgen levels in tissues during ADT, or other androgens in the serum. This study did not measure estrogen levels, although changes in estrogens in addition to androgens may affect prognosis because estrogens might regulate tumor growth in prostate cancer [27]. Furthermore, expressions of the *CYP19A1* gene and aromatase were not examined.

In conclusion, this study is the first to demonstrate that an inherited polymorphism in *CYP19A1* is associated with serum testosterone levels during primary ADT, as well as the risk of progression to castration-resistant prostate cancer

in Japanese men. These findings are consistent with those in Taiwanese, but not North American patients. Taken together, these studies suggest that genetic variation in *CYP19A1* (rs1870050) may affect the prognosis of prostate cancer patients treated with ADT by differentially regulating the serum testosterone level.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval IRB approval from Kyushu University.

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