Review

Gene Polymorphism-related Individual and Interracial Differences in the Outcomes of Androgen Deprivation Therapy for Prostate Cancer

Naohiro Fujimoto,[1] Masaki Shiota,[2] Ikko Tomisaki,[1] Akinori Minato[1]

Abstract

Among patients with prostate cancer, the prognosis after androgen deprivation therapy differs significantly among individuals and among races; however, the reasons underlying these differences are poorly understood. Several single nucleotide polymorphisms in genes associated with prostate cancer progression or castration resistance might serve as the host factor that influences prognosis and, thus, accounts for these individual and racial gaps in treatment outcomes. Accordingly, single nucleotide polymorphisms associated with treatment outcomes could be used as predictive and/or prognostic biomarkers for patient stratification and to identify personalized treatment and follow-up protocols. The present review has summarized the genetic polymorphisms that have been reported to associate with androgen deprivation therapy outcomes among patients with prostate cancer and compared the allele frequencies among different ethnic groups.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: ADT, Gene polymorphism, Oncologic outcome, Prostate cancer, Racial difference

Introduction

Prostate cancer is the most common non−skin cancer affecting men in Western countries,[1] and the incidence and mortality of prostate cancer are increasing in Asian countries.[2] Prostate cancer has been estimated to be the most commonly diagnosed cancer in men in Japan since 2015.[3] Accordingly, the prevention, diagnosis, and treatment of prostate cancer are important public health issues.

Since the introduction of prostate-specific antigen (PSA) screening, for most patients, prostate cancer is diagnosed at curative early stages. However, approximately 10% of patients will have advanced disease at diagnosis. Prostate cancer is a hormone-dependent cancer; the androgen−androgen receptor (AR) axis plays a pivotal role in both disease development and progression. Thus, androgen deprivation therapy (ADT) is effective and has become the standard of care for metastatic prostate cancer. ADT can initially achieve reductions in PSA values and tumor volumes and improvement in symptoms. However, in most patients with advanced prostate cancer, ADT will eventually fail, and disease relapse will occur, resulting in castration-resistant prostate cancer (CRPC).

The prevalence and mortality of prostate cancer varies among different countries and races,[4] and the progression and survival during ADT also differ considerably among races.[5] Several clinical factors, such as the PSA value, cancer stage, Gleason score, and performance status, can affect survival. However, even after adjusting for disease risk, patient characteristics, and ADT method, cancer-specific survival and overall survival (OS) have been better among men treated in Japan than among those treated in the United States.[6,7] In addition, the prognosis differs significantly among patients with prostate cancer who are of the same race and have the same disease stage.

Many genes and alterations thereof are involved in prostate cancer development, progression, and treatment outcomes.[8,9] Potentially, functional polymorphisms of various genes could act as host genetic factors and modify the efficacy of ADT. The present review summarized the results of studies that have investigated the association between genetic polymorphisms and ADT efficacy among patients with prostate cancer and discussed the racial differences in the clinical outcomes of ADT.

[1]Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
[2]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Submitted: Nov 16, 2016; Revised: Jan 6, 2017; Accepted: Jan 10, 2017

Address for correspondence: Naohiro Fujimoto, MD, PhD, Department of Urology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
E-mail contact: n-fuji@med.uoeh-u.ac.jp

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.01.006

Table 1 SNPs in Genes Associated With Clinical Outcome During Androgen Deprivation Therapy

Gene	Function	SNP ID	Genotype (Favorable/Poor)[a]	Associated Clinical Outcome	Reference
CYP17A1	Steroid metabolism	rs743572	GG/AA+AG	TTP	13
CYP19A1	Steroid metabolism	rs1870050	AA/AC+CC	TTP	16
		rs4775936	GG/GA+AA	PCSM	15
HSD3B1	Steroid metabolism	rs1856888	GG/AA+AG	TTP	16
		rs1047303	AA+AC/CC	PFS	17
HSD17B4	Steroid metabolism	rs7737181	CC/GG+CG	TTP	16
AKR1C3	Steroid metabolism	rs12529	GG+GC/CC	PCSM	19
SRD5A2	Steroid metabolism	rs523349	GC+CC/GG	TTP, OS	18
SLCO1B3	Androgen transporter	rs4149117	GG/TG+TT	OS	21
				PCSM	22
SLCO2B1	Androgen transporter	rs12422149	AA+AG/GG	TTP	23
				TTP	24
				PCSM	22
		rs1077858	AA+AG/GG	OS	25
ARRDC3	AR function	rs2939244	AA+AT/TT	PCSM	26
FLT1	AR function	rs9508016	GG/GA+AA	PCSM, OS	26
SKAP1	AR function	rs6054145	CC/CT+TT	PCSM	26
FBXO32	AR function	rs7830622	TT/TC+CC	OS	26
BNC2	ER function	rs16934641	CC/CT+TT	TTP	27
TACC2	ER function	rs3763763	CC/CA+AA	PCSM, OS	27
ALPK1	ER function	rs2051778	GG/GC+CC	OS	27
EGF	Growth factor	rs4444903	AA/GG+GA	TTP	31
TGFBR2	Growth factor receptor	rs3087465	AA+AG/GG	TTP	34
BMP5	Growth factor ligands	rs377444	AA+AG/GG	PCSM, OS	43
YB1	Transcription factor	rs12030724	AT+TT/AA	TTP	40
LSAMP	NF-κB function	rs13088089	AA/AC+CC	PCSM	42
CCL17	NF-κB function	rs223899	CA+AA/CC	PCSM	42
PSMD7	NF-κB function	rs2387084	TT/TG+GG	PCSM, OS	42
MON1B	NF-κB function	rs284924	GT+TT/GG	PCSM	42
IRS2	Intracellular signaling	rs7986346	TT/TG+GG	OS	43
GSTM3	Antioxidation	rs7483	AA/AG+GG	TTP	Unpublished data
CASP3	Apoptosis	rs4862396	TT/TC+CC	OS	43

Abbreviations: ID = identification; NF-κB = nuclear factor-kappa B; OS = overall survival; PCSM = prostate cancer-specific mortality; PFS = progression-free survival; SNP = single nucleotide polymorphism; TTP = time to progression.
[a]Favorable/poor: genotypes associated with favorable or poor clinical outcomes.

Gene Polymorphism and ADT Outcomes

With androgen deprivation, prostate cancer cells become castration resistant by various mechanisms such as maintenance of intratumoral androgens, hypersensitive and promiscuous AR signaling, and AR-independent mechanisms.[8,9] Numerous functional single nucleotide polymorphism (SNPs) in the genes related to these mechanisms could affect the progression of prostate cancer during ADT. We selected SNPs in genes that were reported to be associated with the outcomes of ADT for prostate cancer (Table 1).

Androgen Synthesis and Metabolism

Changes in androgen synthesis and metabolic pathways can strongly affect the progression of prostate cancer and the response to ADT. For example, CYP17A1 is a key enzyme in the androgen synthesis pathway and is overexpressed in CRPC tissues.[10] The maintenance of intratumoral androgens is a possible mechanism underlying castration-resistant tumor growth in cases of metastatic prostate cancer. Abiraterone, a novel CTP17A1-targeting agent, resulted in reduced PSA values and survival benefits in men with CRPC.[11,12] Yamada et al[13] investigated 22 SNPs in 8 genes related to steroidogenesis. Of them, the *CYP17A1* rs743572 AA carriers had significantly worse progression-free survival (PFS) during ADT than did GG carriers ($P = .02$). Furthermore, the serum androgen levels were reported to be higher in men with the *CYP17A1* rs743572 AA/AG genotype than in those with the GG genotype.[14] Thus, these findings suggest that the *CYP17A1* rs743572 AA/AG genotype promotes androgen production and thus facilitates the progression of prostate cancer during ADT. The aromatization of androgens to estrogens has been attributed to CYP19A1. For the related gene, the rs4775936 AA and AG genotypes have been associated with lower serum androstenedione levels, a higher estrone/androstenedione ratio, and significantly worse cause-specific survival during ADT than the GG genotype (52.1 vs. 118.2 months; $P = .04$).[15] A previous study investigating another