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Review article

Prognostic significance of genetic polymorphisms in disease progression and survival in prostate cancer after androgen deprivation therapy☆

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ABSTRACT

It is believed that androgens and their receptors regulate normal prostate growth and mediate prostate cancer development. Androgen deprivation therapy is the most commonly used treatment for advanced prostate cancer. Although the therapy is initially effective, progression of the disease to castration-resistant prostate cancer is almost inevitable, leading to treatment failure. Despite the existence of current clinical parameters, new biomarkers are urgently needed to improve the prognosis. Some molecules and DNA-based genetic biomarkers are under investigation as potential prognostic factors. The advancement in molecular cytogenetic research, such as genome-wide association for single-nucleotide polymorphisms, has made possible the detection of genetic mutations. In this study, a literature search from August 1985 to April 2013 was performed through the PubMed database using the keywords “genetic polymorphisms”, “prostate cancer” and “androgen deprivation therapy”. The results revealed that several genome-wide association studies (such as rs16901979, rs7931342, *HSD17B4*, rs6162 in the *CYP17A1*, rs4243229 and rs7201637 in the *HSD17B2*, rs1062577 in the *ESR1*, *SLCO1B3*, *SLCO2B1*, rs2939244 in the *ARRDC3*, rs9508016 in the *FLT1*, rs6504145 in the *SKAP1*, rs7830611 in the *FBXO32*, rs9508016 in the *FLT1*, rs12529 in the *AKR1C3*, rs16934641 in the *BNC2*, rs3763763 in the *TACC2*, rs2051778 in the *ALPK1*, and rs3763763 in the *TACC2*, *AR*, *ESR1*, and *ESR2*) and single-nucleotide polymorphisms in important pathways (such as androgen signal, biosynthesis, metabolism, androgen receptor binding site, response element, androgen receptor CAG repeat polymorphism length, and estrogen receptor-binding sites) involved in prostate cancer occurrence and mechanism could serve as candidate biomarkers for the early detection of castration-resistant prostate cancer after androgen deprivation therapy. Additional investigations are required to decipher precisely the gene combinations and personalize the management of prostate cancer.

1. Introduction

Due to the early screening of prostate specific antigen (PSA) levels, prostate cancer can be detected at the beginning of its progression. However, 10–20% of newly diagnosed prostate cancer patients are already in the advanced disease stages.[1,2] It is widely accepted that androgen deprivation therapy (ADT) is one of the treatment choices for advanced prostate cancer. ADT can progress

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to a castration-resistant disease within 2–3 years, and the life expectancy of the patient may become only 16–18 months.[2] There are some clinical prognostic factors, such as tumor stage, Gleason score, and PSA kinetics, for the presentation of the disease; however, a proper surrogate for predicting survival remains unknown. The clinical stage incorporation of genetic markers has been proposed by some investigators. Previous studies[3–13] have shown that germline genetic variants have the potential to identify predisposition to aggressive prostate cancer. This complex disease still needs further elucidation of the biological pathways involved in its initiation and progression.

The purpose of this mini-review article was to investigate previous reports regarding the prognostic significance of genetic polymorphisms on disease progression and survival after ADT.

2. Materials and methods

The PubMed database was searched from August 1985 to April 2013 for related articles using the keywords “genetic polymorphisms”, “prostate cancer” and “androgen deprivation therapy”. Only articles in English and including human participants were included in the current literature review. The articles related to the keywords genetic polymorphism, androgen deprivation therapy, and prostate cancer were additionally collected in this study. In total, 21 articles were identified and included in this mini-review.

3. Results and discussion

3.1. Prostate cancer susceptibility variants

The risk of prostate cancer has recently been identified by several genome-wide association studies (GWASs). However, Asian male patients receiving ADT have not been evaluated for the risk variants in advanced prostate cancer. Bao et al[4] analyzed 19 prostate cancer susceptibility variants as prognostic predictors for survival after ADT. Their study cohort collected 601 prostate cancer patients treated with ADT. Prostate cancer-specific mortality (PCSM) and all-cause mortality (ACM) after ADT were assessed by Kaplan–Meier analysis and Cox's regression model. Two polymorphisms, rs16901979 and rs7931342, were significantly associated with PCSM ($p = 0.005$ for rs16901979 and $p = 0.038$ for rs7931342), and rs16901979 was also associated with ACM ($p = 0.003$) following ADT. It has been reported that the effect of rs7931342 is influenced by other known clinical factors and that rs16901979 remains a significant predictor for PCSM and ACM after ADT ($p = 0.002$). Furthermore, the risk evaluation of PCSM and ACM in high-risk patients with distant metastasis ($p < 0.017$) can be increased by combination of rs16901979 status and the current clinical staging system.

3.2. Genetic polymorphism in androgen signaling, biosynthesis, and metabolic pathway

It is believed that the development of normal prostate and prostate cancer is highly associated with androgen levels. Therefore, the androgen receptor (AR), a nuclear receptor superfamily, plays a critical role in mediating the biological effects of androgen.[14] Gene expression mediated by the promoter region of androgen-responsive genes in target tissues[14] is regulated by the androgen–AR complex that interacts with co-regulators and binds to specific androgen-responsive elements (AREs). In a study by Ross et al,[5] a cohort of 529 advanced prostate cancer patients treated with ADT were genotyped for 129 DNA polymorphisms distributed across 20 genes involved in androgen metabolism. The authors hypothesized that the efficacy of ADT could be improved by germline genetic variations in the androgen axis. Three polymorphisms in separate genes (*CYP19A1*, *HSD3B1*, and *HSD17B4*) were considered significant ($p < 0.01$) by multivariate analyses associated with time to progression (TTP) during ADT. Patients with more than one polymorphism were associated with improved TTP and a better response to therapy ($p < 0.0001$). The pharmacogenomics on an individual's response to ADT were influenced by an inherited variation of the androgen metabolic pathway. Two separate cohorts were examined by Lévesque et al.[6] They enrolled 526 Caucasian men with organ-confined prostate cancer and 601 Taiwanese men on ADT. There were 109 haplotype-tagging single-nucleotide polymorphisms (SNPs) in *CYP17A1*, *ESR1*, *CYP19A1*, and *HSD3B1* tested in Caucasians. Kaplan–Meier survival curves and Cox's regression models were used for the prognostic significance on disease progression. Then, the authors tested their findings, including the previous positive ones, in Taiwanese men ($n = 32$ SNPs). They used specific and sensitive mass-spectrometry-based methods to evaluate the influence of these markers on the circulating hormonal levels. In both cohorts, variants of *CYP17A1* (rs6162), *HSD17B2* (rs4243229 and rs7201637), and *ESR1* (rs1062577) were related to disease progression. These variations were highly related to the progression of the disease in Caucasians (hazard ratio: 2.29–4.10; $p = 0.0014–2 \times 10^{-7}$) and survival rate in Taiwanese populations (hazard ratio = 3.74; 95% confidence interval = 1.71–8.19, $p = 0.009$). Plasma dehydroepiandrosterone sulfate levels were influenced by the *CYP17A1* rs6162 polymorphism ($p = 0.03$), dihydrotestosterone by the *HSD17B2* rs7201637 ($p = 0.03$), and estrone-S and androsterone–glucuronide by the *ESR1* rs1062577 ($p \leq 0.05$). This study showed that *CYP17A1*, *HSD17B2*, and *ESR1* could be candidate prognostic factors for prostate cancer progression in different ethnic groups and even in different disease stages.

3.3. SLCO2B1 and SLCO1B3

Wright et al[7] studied the efficacy of ADT in prostate cancer patients through genetic variation in *SLCO1B3* and *SLCO2B1*. The genetic variation of SLCO genes may modify androgen uptake. They found that the genetic variation between castration-resistant prostate cancer (CRPC) metastases patients and primary prostate cancer patients are associated with high *SLCO1B3* and *SLCO2B1* expression. The overexpression of these variants was also associated with the elevated risk of PCSM. Yang et al[8] investigated genotype *SLCO2B1* and *SLCO1B3* SNPs in a cohort of 538 patients with prostate cancer treated with ADT. They found that TTP on ADT was highly related to three SNPs in *SLCO2B1* ($p < 0.05$). It took 10 months to reveal the differences in median TTP for each of these polymorphisms. The *SLCO2B1* genotype plays a vital role in enhancing the efficient import of androgen, thus accelerating cell growth, which is associated with a shorter TTP on ADT. A median 2-year shorter TTP on ADT was noted for patients carrying both *SLCO2B1* and *SLCO1B3* genotypes. The capability for transporting dehydroepiandrosterone sulfate into the cells was increased in SLCO2B1-312Arg-variant LNCaP cells.

3.4. AR binding site

Recent studies have shown that prostate tumor progression is mediated by AR binding to AREs in the genome.[2,3,14] Huang et al[9] studied the relationship between the genetic variants in AREs and the clinical outcomes after ADT in prostate cancer patients. They included 601 prostate cancer patients treated with ADT. Fifty-five SNPs were investigated in the genome-wide *in silico*-predicted AREs. After adjusting for several known prognostic factors, *ARRDC3*