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 HSD17B1, rs1062577 in the ESR1, SLCO1B3, SLCO2B1, rs2593244 in the ARRD3, rs9508016 in the FLT1, rs6504145 in the SKAPI, rs7830611 in the FBXO32, rs9508016 in the FLT1, rs12529 in the ARRD1C, 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. It is widely accepted that androgen deprivation therapy (ADT) is one of the treatment choices for advanced prostate cancer. ADT can progress
to a castration-resistant disease within 2–3 years, and the life expectancy of the patient may become only 16–18 months. 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 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 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. Gene expression mediated by the promoter region of androgen-responsive genes in target tissues 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., 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. 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 × 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 < 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. 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. 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. Huang et al. 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
rs2939244, FLT1 rs9508016, and SKAP1 rs6504145 were still significant predictors for PCSM, and FBXO32, rs7830622, and FLT1 rs9508016 remained significant predictors for ACM in multivariate analysis. Furthermore, there were strong combined genotype effects on PCSM and ACM (p < 0.001).

3.5. G/A polymorphism in the ARE1 of the PSA gene

PSA gene expression is regulated by AR through AREs present in the promoter region of the gene. The substitution of G to A at position 158 in ARE of the PSA gene has been speculated in some reports. Shibahara et al showed no difference in the promoter activity and binding capacity of the AR in vitro between the two alleles in the Japanese population. Polymerase chain reaction amplification and restriction digestion assays were performed in 101 patients who underwent radical prostatectomy, thus showing PSA–158 G/A polymorphism. The homozygosity for the A allele is less common in the Japanese population than that in other ethnic populations. The serum PSA level did not show any differences in the differentiation of cancer, pathological stages, cancer volume, or ratio of serum PSA/cancer volume at the time of diagnosis. It is notable that after neoadjuvant endocrine therapy, cancer volume was significantly smaller in the GG genotype than that in the AA + AG genotype. Therefore, their study showed no effect on the PSA promoter activity in vitro and no association with the serum PSA level in the PSA–158 G/A polymorphism in Japanese men. However, the patients with the GG genotype of ARE1 may be more sensitive to androgen ablation therapy.

3.6. AR CAG repeat polymorphism length

ADT has shown the ability to suppress androgen production or AR activity. However, aggressive CRPC is often observed after ADT. Several possible mechanisms were proposed to explain the development of CRPC. Low androgen levels can also activate AR responses by the alteration of transcriptional coactivators and activation of signaling pathways. There were no significant differences in intraprostatic androgens between castrated men with CRPC and that of men with a normal prostate. The cancer cells may produce intracellular hormones to promote their own growth. Therefore, many studies focus on the sex hormone metabolic pathways and genetic variants as predictive factors. Yu et al investigated whether the host genetic variations in sex hormone pathway genes are associated with the efficacy of ADT. There were 18 polymorphisms across 12 key genes involved in androgen and estrogen metabolism included in a cohort of 645 patients with advanced prostate cancer treated with ADT. The results showed that AKR1C3 rs12529 and AR CAG repeat length remained significantly associated with PCSM after ADT (p < 0.041). In addition, a 13.7-fold increased risk of PCSM was found in individuals carrying two unfavorable genotypes at these loci than those carrying no unfavorable genotypes (p < 0.001). Two candidate molecular markers in the key genes of androgen and estrogen pathways associated with PCSM after ADT were identified to establish the role of pharmacogenomics in this therapy.

3.7. Genetic polymorphisms in estrogen receptor binding sites versus inherited variation of the AR, ESR1, and ESR2 genes

Recent reports have demonstrated that estrogen and its corresponding receptor are correlated with prostate cancer development and progression. The main biological effects are mediated by the binding to estrogen response elements (EREs) in the regulatory regions of the target genes. The variety of sequences in EREs might be associated with estrogen receptor–ERE physiological activities. Huang et al used a genome-wide database in a cohort of 601 men with advanced prostate cancer treated with ADT by evaluating 49 ERE SNPs. The result showed that BNC2 rs16934641 was highly associated with disease progression; furthermore, TACC2 rs3763763 was correlated with PCSM, and ALPK1 rs2051778 and TACC2 rs3763763 were correlated with ACM. In multivariate analysis, these SNPs remained significant because they included known clinical pathological predictors. Moreover, the combination of the genomic effect was observed on ACM when ALPK1 rs2051778 and TACC2 rs3763763 were both present. Patients who had more unfavorable genotypes had a shorter time to ACM during ADT (p < 0.001). Therefore, ERE SNPs may correlate with known predictors and improve the outcome prediction in patients with prostate cancer receiving ADT.

By contrast, commonly inherited variation in the AR, ESR1, and ESR2 genes, studied by Sun et al to investigate the risk of developing aggressive prostate cancer and the response to ADT in a hospital-based cohort, showed different results. There were 43 tagging SNPs covering the loci of AR (n = 4), ESR1 (n = 32), and ESR2 (n = 7) successfully genotyped in 4073 prostate cancer patients. None of these SNPs were correlated with disease severity by evaluating the D’Amico risk classification, pathological stage, or the response to ADT. The study revealed no statistical difference between common genetic variations in AR, ESR1 or ESR2 and prostate cancer severity or response to ADT.

4. Conclusion

The discovery of genetic variants from several genome-wide association studies and of SNPs involved in the critical pathways of prostate cancer occurrence and mechanism could serve to identify candidate biomarkers for the early detection of the progression of the disease to CRPC after ADT. Clinical implications from these studies may play a critical role in predicting the responses to ADT. Additional investigations are required to decipher precisely the gene combinations and personalize the management of prostate cancer.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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