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Review

Molecular alterations and emerging targets in castration resistant prostate cancer

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Abstract Prostate cancer is the most common malignancy in Western Europe, of which approximately 10–20% presents with advanced or metastatic disease. Initial response with androgen deprivation therapy is almost universal, but progression to castration resistant prostate cancer (CRPC), an incurable disease, occurs in approximately 2–3 years.

In recent years, the novel taxane cabazitaxel, the hormonal agents abiraterone and enzalutamide, the immunotherapeutic agent sipuleucel-T and the radiopharmaceutical radium-223 have been shown to prolong survival in large randomised trials, thus widely increasing the therapeutic armamentarium against the disease. Despite these advances, the median survival in the first-line setting of metastatic castration-resistant prostate cancer (mCRPC) is still up to 25 months and in the post-docetaxel setting is about 15–18 months.

There is an urgent need for the development of biomarkers of treatment response, and for a deeper understanding of tumour heterogeneity and the molecular biology underlying the disease. In this review, we attempt to provide insight into the novel molecular targets showing promise in clinical trials.

1. Introduction

Prostate cancer is the most common malignancy in men in Western Europe with 93.1 new cases per 100.000 inhabitants in 2008 [1], of which approximately 10–20% present with advanced-metastatic disease. Initial response with androgen deprivation therapy is almost universal, but progression to castration resistant prostate cancer (CRPC), an incurable disease, occurs in approximately 2–3 years [2]. Until 2010, docetaxel was the only agent with proven survival benefit in CRPC [3]. Since then, the chemotherapeutic agent cabazitaxel [4], the hormonal agents abiraterone [5] and enzalutamide [6], the immunotherapeutic agents sipuleucel-T [7] and the radiopharmaceutical radium-223 [8] have been shown to prolong survival, widely increasing the therapeutic armamentarium (see Fig 1, Tables 1-2).

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Despite these advances, the median survival of metastatic castration-resistant prostate cancer (mCRPC) is still up to 25 months in the first-line setting [7,9] and about 15–18 months the post-docetaxel setting [5,6]. There is an urgent need for the development of biomarkers of treatment response and for a deeper understanding of tumour heterogeneity and the molecular biology underlying the disease. In this review, we attempt to provide insight into novel molecular targets showing promise in clinical trials. Other relevant topics in drug development for prostate cancer such as epigenetics and immunotherapy, reviewed in detail elsewhere [10–12], were considered outside the scope of this review.

2. Methods

A review of the literature searching Pubmed and major cancer conferences was performed in May 2013. The search strategy included the terms metastatic prostate cancer, castration resistant prostate cancer, molecular biology, androgen receptor, phosphoinositide 3-kinase (PI3K), poly (ADP-ribose) polymerase (PARP), MET, angiogenesis and SRC.

3. Common genomic aberrations in prostate cancer

Molecular studies have identified potentially relevant genomic alterations in human prostate cancer, some of which are associated to key regulatory genes [13] (see Table 3). These include loss of chromosome 8p (NKX3.1), the most frequent alteration in the prostate onco-genome; deletion of phosphatase and tensin homologue (PTEN) on 10q23.31; Retinoblastoma tumour (RB1) on 13q14.2; TP53 on 17p31.1; and the interstitial 21q22.2-3 deletion spanning ERG and TMPRSS2 [14]. Although the overall mutation rate in CRPC is low, mutations in SPOP, MED12, p53, in the histone-modifying MLL2 and the pioneer factor FOXA1 genes can play a role as can androgen receptor (AR) mutations in castration resistant disease [15,16].

The NKX3.1 gene, located in chromosome 8p21, a region with a high rate of LOH, encodes a tumour-suppressor protein that is postulated to decrease cell survival by enhancing ATM activity after DNA damage [17]. Loss of 8p21 is an early event in prostate carcinogenesis [18]. The Myc oncogene is located in 8q24, a broad amplicon that contains multiple genes associated with prostate cancer [13]. The role of c-Myc as a ligand-independent AR target gene has been proposed although this remains controversial [19]; studies report no effect of the androgen ligand R1881 or the antiandrogen MDV3100 on c-Myc expression in cell lines [20]. Recently, the BET bromodomain inhibitor JQ1 [21] was reported to suppress c-Myc overexpression and cell proliferation. P53 (17p31) has an essential role in the transcription of genes involved in apoptosis, cell cycle arrest and DNA repair. P53 alterations have been associated with recurrence after radiation and androgen suppression [22] as well as reduced docetaxel-induced apoptosis [23]. Retinoblastoma tumour (RB1) suppressor gene pathway aberrations have been identified in 34% of primary and 74% of metastatic prostate cancers [14]. Loss of RB1 function may be linked to castration resistance through activation of AR signalling by unsuppressed E2F transcription factors [24]. A differential therapeutic approach has been proposed, where CDK inhibitors could enhance AR suppression in RB positive while RB negative tumours could be particularly susceptible to radiotherapy or DNA damaging agents [25].

Deletions in the CHD1 gene (5q21) have been identified in 10–17% of prostate tumour samples, possibly second only to PTEN loss as the most frequently homozygously deleted gene in the prostate cancer genome, increasing invasiveness in prostate cancer cell lines [26,27]. CHD1 deleted tumours appear to have a high frequency of intrachromosomal rearrangements and may have a worse prognosis.

3.1. ETS fusion positive prostate cancers

The ERG oncogene is one of the most frequently expressed genes in prostate cancer [28], and its fusion to the TMPRSS2 gene is a common and probably early event in prostate carcinogenesis [29]. Members of the ETS family of transcription factors (ERB, ETV1, ETV4) are placed under the control of the TMPRSS2 promoter which is activated by AR signalling [30]. ERG can disrupt AR signalling through epigenetic silencing of target genes, and ETS activation may promote epithelial-mesenchymal transition (EMT) and tumour-invasive properties [31]. The presence of ERG rearrangements has been associated with higher response-rates to abiraterone [29].

3.2. ETS fusion negative prostate cancer

Recent studies have identified aberrations that are mutually exclusive with ETS fusions. SPOP mutations characterise a distinct subtype of ETS negative prostate cancer that has been associated with recurrent somatic deletions at 5q21(CHD1) and 6q21(FOXA1) [16]. Up to 96% of tumours with CHD1 deletion are ETS rearrangement negative, possibly identifying ETS-/CHD- tumours as a distinct molecular subtype [15].

Overexpression of SPINK-1, a trypsin inhibitor associated with bad prognosis in multiple malignancies [32] is mutually exclusive with ERG/ETV1 overexpression and defines an aggressive molecular subtype [33]. Knockdown of SPINK-1 is able to inhibit cell proliferation and invasion in xenograft models [34].

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