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The Androgen Receptor in Castration-Resistant Prostate Cancer: Still a Clinical Opportunity?

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Prostate cancer is a leading cause of cancer death in men, with an estimate of about 241,000 new cases and 34,000 deaths due to prostate cancer in the United States in 2011 [1]. Prostate cancer is dependent on the androgen receptor (AR); the androgen axis shown to be a key driver of the disease [2]. This principle was first established more than 70 years ago by the demonstration that surgical castration will retard the progression of disease [3]. Prostate cancer typically responds well to suppression of testosterone. Surgical castration is effective in lowering testosterone production but suffers from its psychological impact and irreversibility; thus treatment of the early stages of advanced disease in the Western world is typically based on 'chemical' castration with luteinising hormone releasing hormone (LHRH) agonists. These agents suppress luteinising hormone release and markedly reduce testicular testosterone production. Even with effective surgical or chemical castration, however, some residual androgen production persists (perhaps within tumor cells themselves or from extra-testicular sources); hence there has been a search for other agents to manage the disease.

More recently, AR blockade therapies have been developed, and these agents are now also commonly used to manage prostate cancer. These act by blocking the stimulatory action of testosterone on cells via a direct antagonist action on the AR. In advanced progressive prostate cancer, an LHRH agonist and anti-androgen therapy are frequently combined (often termed 'maximum androgen blockade'). Ultimately, however, advanced prostate cancer becomes resistant to these treatments and progresses, becoming castration-resistant prostate cancer (CRPC) [2]. Still, even at this stage, CRPC seems largely to be driven by the AR, and therapy continuing to target the androgen axis offers promise for delaying further disease progression. A number of agents or therapies targeting the AR axis have recently been shown to provide clinical benefit in trials. In this report we provide a brief overview of the AR, followed by a discussion of new and investigational second generation agents which continue to target the receptor and the androgen axis as treatment of CRPC. It was not our intent, however, to provide an exhaustive review of all anti-androgen therapies.

The AR is a member of a nuclear hormone receptor superfamily that regulates target gene expression [4]. Two AR target genes that have been well characterized include *KLK3* regulating prostate specific antigen (PSA) and *TMPRSS2-ETS* fusion genes; control of these genes includes regulation by the AR, DNA-binding transcription factors and other co-regulatory factors [5-7]. In androgen-dependent prostate cancer, the AR is known to promote cell proliferation through regulation of G1/S transition in the cell cycle, but only in the presence of androgen [8]. In androgen-independent prostate cancer, however, the AR appears to remain active through a variety of potential mechanisms including mutation and amplification of the AR, local production of androgens, increased androgen sensitivity and activation by growth factors [9-11]. In androgen-independent prostate cancer cells, the AR up-regulates M-phase cell cycle genes, including UBE2C, a gene which inactivates the checkpoint of the M-phase; a similar up-regulation was not seen in cells which were androgen-dependent [12]. Histone H3K4 methylation and FoxA1 transcription factor binding appear in androgen-independent cells and drive UBE2C activation. The authors concluded that the AR regulates a distinct transcription program in androgen-independent prostate cancer [12].

During the development of the prostate and prostatic epithelium, effects of androgens are thought to be due to stromal AR [13]. With the transformation of the normal prostate cell to a cancerous one, it is believed that there is a change in AR signaling from a paracrine mechanism to one that is autonomous within the cell [14,15]. Intra-epithelial neoplastic transformation is a recognized precursor to prostate cancer [16], and such transformation may be initiated, for example, by cell-autonomous AKT activation or by paracrine fibroblast growth factor induction dependent on epithelial AR signaling [17]. The AR appears to serve multiple functions, and may serve both to promote proliferation and survival in stromal and epithelial luminal cells, respectively, or to suppress metastasis in epithelial basal cells [18].

Once established, prostate cancer remains dependent on androgen signaling through the AR. The AR is essential for prostate cancer growth both while it is amenable to androgen blockade and after it progresses to CRPC [11]. Although CRPC is often considered as androgen-independent since most cases progress even in the face of castrate levels of testosterone [19], it commonly remains hormone driven [20,21]. AR protein is expressed in a great majority of prostate cancer, both in the androgen-dependent and -independent states [19]; reductions of AR protein reduce growth of both in experimental models [22,23]. Changes in AR signaling during progression to CRPC are common, and AR is frequently overexpressed in CRPC [22,24,25]. Intratumoral levels of androgens are high with continued activation of the AR in CRPC despite low circulating androgens; tumor cells may independently synthesize androgens *de novo* [26,27]. CRPC cells with

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high levels of AR may be rendered hypersensitive even to reduced levels of androgens [28,29]. Other mechanisms that could keep AR signaling elevated in CRPC include mutations in the AR [30], splice variants [31] or changes in coregulatory proteins [32]. Thus, AR signaling appears to play a critical role in prostate cancer, and the AR is an attractive target for therapy for CRPC. Since the observation of a survival benefit in CRPC with docetaxel in 2004 [33], there has been a keen interest in agents that target the androgen axis for treatment of CRPC. A brief discussion of new and investigational agents in this regard follows below.

Abiraterone

Abiraterone is a potent and irreversible inhibitor of the enzyme 17 α-hydroxylase/C17,20 lyase (CYP17), the catalyst for the two essential steps of androgen biosynthesis: (1) the conversion of pregnenolone and progesterone to their 17 α-hydroxyderivatives; and (2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione [34], precursors of testosterone. Since CYP17 is expressed in testicular, adrenal and prostatic tissues, it was hypothesized that abiraterone may be effective in CRPC by inhibiting the extragonadal production of androgen that could potentially drive CRPC progression [20].

Abiraterone acetate was tested in a number of Phase I and II studies to evaluate initial safety and tolerability [20,35-39]. In a Phase III trial, 1195 post-docetaxel CRPC patients were randomized 2:1 to study treatment with 5 mg prednisone twice daily and either abiraterone acetate 1000 mg or placebo once daily, respectively [40]. Treatment with abiraterone acetate with prednisone versus placebo with prednisone resulted in a 36% increase in median survival (14.8 vs 10.9 months) and a 35% reduction in the risk of death (hazard ratio, 0.65; 95% CI, 0.54 to 0.77; P<0.001), respectively [40]. Additionally, study treatment versus placebo resulted in an improvement in progression-free survival (5.6 vs 3.6 months; P<0.001), time to PSA progression (10.2 vs 6.6 months; P<0.001), and PSA response rate (29% vs 6%; P<0.001), respectively. Adverse events reported more frequently in the treated group compared with placebo included fluid retention, hypertension and hypokalemia [40]. On the basis of these Phase III results, abiraterone acetate was initially approved for use in the United States in April, 2011 [41], and subsequently in Europe in September, 2011 [42], in the post-docetaxel setting. Another Phase III study is underway in patients not yet treated with chemotherapy (Clinicaltrials.gov registry number: NCT00887198).

The activity of abiraterone demonstrated that targeting the androgen axis is still an effective treatment strategy for prostate cancer even after it has progressed to a castration-resistant state. Unfortunately, resistance to abiraterone acetate may develop, and a recent preclinical study has suggested that this resistance may develop due to up-regulation of CYP17 or the induction of the AR or variants that promote ligand-independent activation [43]. The appearance of abiraterone resistance suggests the potential for combination therapy with an agent that directly targets the AR as a possible therapeutic strategy to decrease the development of resistance to abiraterone acetate.

MDV3100

MDV3100 (Medivation, Inc., San Francisco, CA, USA/Astellas Pharma Inc, Tokyo, Japan) is an AR antagonist designed to improve binding affinity and reduce agonist activity compared with available therapies [44]. It has a higher affinity for the AR versus bicalutamide, reduces nuclear translocation, DNA binding and coactivator recruitment and may increase apoptosis; additionally, it appears to be devoid of any agonist activity [44,45]. In a Phase I-II study, 140 patients with metastatic CRPC were enrolled in ascending dose cohorts and treated with doses ranging from 30-600 mg administered once daily (maximum tolerated dose: 240 mg) [44]. There was preliminary evidence for response to therapy [reduction in PSA of ≥ 50% (56% of patients); soft tissue response (22% of patients); stabilized bone disease (56% of patients); and improvement in circulating tumor cell (CTC) counts (49% of patients)]. On the basis of these encouraging results, a number of Phase II trials and a Phase III registration trial were started.

The Phase III AFFIRM trial of MDV3100 (registry number: NCT00974311) enrolled 1,199 men with advanced prostate cancer who had been previously treated with docetaxel-based chemotherapy. An interim analysis showed that the study had met its pre-specified efficacy stopping criteria, evidencing a significant improvement in overall survival compared with placebo (18.4 vs 13.6 months, respectively; P<0.0001), with a 37% reduction in risk of death (HR: 0.63) [46]. As a result, the study was stopped early by the Independent Data Monitoring Committee, and men randomized to placebo were offered therapy with MDV3100 [46]. A Phase III trial (PREVAIL) is ongoing in men with advanced prostate cancer who have not yet received chemotherapy (registry number: NCT01212991). The ongoing Phase II TERRAIN trial (MDV3100 compared with bicalutamide) is studying men who have progressed while on LHRH analogue therapy or following surgical castration (registry number: NCT01288911). Hormone-naïve patients are currently being studied in a Phase II trial to evaluate MDV3100 monotherapy (registry number: NCT01302041).

TAK-700

Tak-700 (ortoronel; Millenium Pharmaceuticals, Cambridge, MA, USA/Takeda, Osaka, Japan) is an orally available, selective inhibitor of CYP17. In preliminary results from a Phase II trial of patients with metastatic CRPC, TAK-700 resulted in a dose-dependent decrease in androgen levels and in PSA reductions of at least 50% in a majority of patients [47]. TAK-700 administered with prednisone is being studied in an ongoing, placebo-controlled, Phase III clinical trial in patients with metastatic CRPC who are naïve to chemotherapy; primary endpoints are overall survival and radiographic progression-free survival (registry number: NCT01193244). A second placebo-controlled Phase III trial of TAK-700 adminstered with prednisone is ongoing in patients with metastatic CRPC who had previously received chemotherapy with docetaxel (registry number: NCT01193257). The primary outcome measure is overall survival.

TOK-001

TOK-001 (galeterone; Tokai Pharmaceuticals, Cambridge, MA) is an orally available CYP17 inhibitor with additional direct AR antagonist activity [48,49]. A Phase I trial (ARMOR1) to evaluate safety (primary objective) and preliminary efficacy (secondary) in patients with CRPC who are chemotherapy-naive is ongoing (registry number: NCT00959959).

ARN-509

ARN-509 (Aragon Pharmaceuticals, Inc, San Diego, CA, USA) is a novel AR antagonist [50]. It is being studied in an ongoing Phase I/II trial to assess safety and preliminary efficacy in patients with progressive, advanced CRPC (registry number: NCT01171898). The

Phase II portion of the trial has three arms to assess ARN-509 in (1) non-metastatic, treatment-naive CRPC with rapidly rising PSA; (2) metastatic, treatment-naive CRPC; and (3) post-abiraterone but chemotherapy-naive metastatic CRPC. The primary outcome is PSA response, as the percentage of patients reaching at least a 50% reduction in PSA compared with baseline at 12 weeks.

AZD3514

AZD3514 (AstraZeneca, London, United Kingdom) is an orally available, AR down-regulator, therapy which could act on activation of the AR via ligand-independent mechanisms [43,50]. Phase I trials to evaluate safety (primary objective) and preliminary efficacy (secondary) in patients with progressive, metastatic CRPC are ongoing in Europe (registry number: NCT01162395) and Japan (registry number: NCT01351688).

In summary, therapy directed at the androgen axis has been a mainstay of the management of prostate cancer for decades. It is clear that, although the biology of the AR is complex and still evolving, the AR is a key player in the initiation and progression of prostate cancer and remains as a critical component for the progression of CRPC (for recent reviews, see Ryan and Tindall [49] and Attard et al. [50]). Indeed, the evidence supports that the AR remains a key driver of the disease even after it has progressed and become castration-resistant. Multiple new agents that target the AR or the androgen axis have either become available or are investigational for the treatment of CRPC. Different agents used either in combination or in specific sequence may aid in therapy by combating the resistance that can develop with single agent therapy. Additionally, the development of other endpoints, such as CTC counts, may help to address the challenge posed by the need to meet the regulatory demand for overall survival (OS) data. CTC counts have been reported by a number of investigators to be associated with OS [51-53]. Further clinical trials will be required to address these hypotheses. Our view is that there is real promise for the availability of more tools in the near future for the clinical management of prostate cancer.

Conflict of Interest

Dr. Finkelman and Dr. Clack are full time employees of AstraZeneca and own stock in AstraZeneca.

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