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Novel Androgen Deprivation Therapy (ADT) in the Treatment of Advanced Prostate Cancer

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Abstract

Androgen deprivation therapy has been the mainstay of treatment for advanced and metastatic prostate cancer. The use of novel agents targeting the androgen receptor and its signaling pathways offers a promising approach that is both safe and effective. We describe the rationale behind the use of these compounds in clinical development and the existing challenges as to how best to incorporate these new and emerging therapies in the changing treatment paradigm of metastatic prostate cancer.

Introduction

Prostate cancer remains the most common non-cutaneous malignancy among American men. In 2010 alone, about 217,730 will be diagnosed with prostate cancer and about 32,050 will die of the disease [1]. Majority of prostate cancers diagnosed in the early stage are cured. However, about a third of patients may recur with biochemical recurrence [2]. While the natural history can be protracted, some patients will present with metastatic disease and eventual castration resistance occurs. Androgen deprivation therapy (ADT) remains the cornerstone of treatment for advanced and metastatic prostate cancer ever since the link between androgen dependency and prostatic growth was established [3]. While the response to hormonal therapy is effective and almost universal, the durability of response is variable. Eventual castration-resistance occurs via androgen-dependent and independent pathways [4]. Once castration resistance emerges, few therapeutic options exist. For metastatic, especially symptomatic patients, chemotherapy with docetaxel and prednisone has been used given the overall survival data from TAX327 [5]. The year 2010 has also brought forth several exciting developments and approvals from the United States Food and Drug Administration (FDA) for the treatment of advanced prostate cancer. Sipuleucel-T (Provenge®; Dendreon Corp., Seattle, WA) is a therapeutic cancer vaccine that is the first of its kind to be approved by the FDA for the treatment of asymptomatic or minimally

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symptomatic metastatic prostate cancer, based on a 4.1 month survival benefit from the IMPACT trial [6]. No standard 2nd line chemotherapy existed until June 2010, when cabazitaxel (Jevtana®; Sanofi-Aventis, Bridgewater, NJ) was similarly approved by the FDA for patients who received prior docetaxel. Amidst these drug approvals, several other agents in development have shown promise in this population, and are in the final phases of development. Among these promising agents include novel androgen antagonists and strategies to target the androgen receptor (AR) signaling pathway that serve as second-line hormonal manipulation. This review will focus on the biologic rationale as well as progress in the field with the use of novel anti-androgen therapy post-docetaxel failure.

Background on the use of Androgen Deprivation Therapy

ADT is achieved through several methods, although the use of chemical castration with Gonadotropin Releasing Hormone Agonists (GnRH-A) and antagonists have been used with wider acceptance compared to surgical castration. Nonsteroidal anti-androgens have also been used as monotherapy in those who wish to maintain potency and quality of life, as well as in conjunction with ADT, termed combined androgen blockade (CAB). However, the use of CAB offers survival advantage of only about 2 – 3% [7], but at increased cost and toxicity. While most patients will respond to ADT, castration resistance eventually ensues. The use of first line hormonal therapy refers to the primary use of ADT. Further hormonal manipulation beginning with anti-androgen withdrawal is often employed as a first step in response to castration resistance. Henceforth, second-line hormonal manipulation is undertaken to achieve additional prostate specific antigen (PSA) responses.

Mechanisms of Castration-Resistance

The term “castration-resistance” has evolved after initial observations that the use of conventional secondary hormonal therapies such as ketoconazole, alternative anti-androgens, aminoglutethimide, provided continued clinical response despite initial progression on androgen deprivation therapy. Terms such as “androgen-independence”, “hormone-resistance”, “hormone-refractory” were gradually supplanted by “castration – resistant” prostate cancer (CRPC), defined as a progressive rise in PSA despite castrate levels of testosterone, which typically is less than 50 ng/dl but preferably less than 20 ng/dl [8]. The name change is more than just a terminology change. Biologically, the mechanisms that underlie the progression of hormone dependent prostate cancer to one of castration resistance involve regulation at the androgen receptor (AR) level. Androgen deprivation therapy (ADT) reliably decreases serum testosterone in > 90% of cases but intra-tumoral decline in androgen levels are less dramatic [9,10]. Therefore, this allows expression of AR and other androgen-responsive genes unchanged. Previous studies of prostate cancer cell lines showed that the AR is persistently up-regulated during progression [11]. Various pathways have been described in bringing about castration resistance [4]. Several involve the AR signaling pathway which includes *de novo* or intratumor-derived androgens that signal and activate the AR, AR overexpression or amplification, AR upregulation at the transcriptional levels, change in co-factor levels, and promiscuity of the AR in binding with other ligands [12]. Others involve bypassing the AR and includes deregulation of genes involved in apoptosis (including Bcl-2 and PTEN – phosphatase and tensin homologue via Akt-activation [13].

Understanding the pathways involved in the intratumoral or *de novo* production of androgens that could continuously trigger AR signaling helps in determining the potential targets for therapy in castration resistant prostate cancer. While majority of androgens are testicular in origin, adrenal sources of androgen that is independent of the luteinizing hormone control make up an important source of residual androgens that can trigger the AR.

Adrenal androgens are synthesized in a series of multi-step enzyme conversions that result from conversion of cholesterol to pregnenolone through side-chain cleavage by members of the cytochrome P450 family, specifically, CYP11A1. CYP17A1 with 17-hydroxylase and 17,20-lyase enzymatic function further catalyzes pregnenolone to 17-hydroxypregnenolone and subsequently to dehydroepiandrosterone (DHEA), which can be further converted to the testosterone precursors, 5-Androstenediol and androstenedione through the type II 3β-hydroxysteroid dehydrogenase (3B-HSD) enzymes. It is important to note that the CYP17A1 enzyme is critical in the production of glucocorticoids but not in mineralocorticoid production. Testosterone gets converted to dihydrotestosterone, the more potent form of testosterone, via 5 alpha reductase, but both can bind to the AR and trigger the androgen receptor elements (AREs), which leads to the activation of the AR-regulated genes. Interventions at any route along these pathways therefore provide innovative means of targeting castration resistant prostate cancer.

Strategies in circumventing the AR

a. Anti-androgen withdrawal and secondary hormonal manipulation

The use of ADT is effective though resistance invariably develops within 12 to 33 months [14]. The anti-androgen withdrawal response has been described in the 1990's and was employed to achieve response in about a third (on occasion even up to 75%) of patients [15-17]. While the exact mechanism of anti-androgen withdrawal response is not quite understood, several hypotheses have been described [18,19]. It is generally felt to be secondary to the switch from androgen antagonist to agonist activity with alteration in the androgen receptor coactivator and corepressor recruitment due to mutations in the AR-ligand binding domain [20,21], such that resistance to antiandrogens are conferred by amplification of signals even from low levels of circulating residual ligand [11]. Anti-androgen withdrawal is therefore one of the first steps clinicians undertake when castration resistance develops. However, response to anti-androgen withdrawal lasts for only a few months [16], though occasionally observed up to over a year [15].

Nevertheless, it is an approach being undertaken; be it alone or in combination with a secondary hormonal manipulation, such as the concomitant use of ketoconazole. The Cancer and Leukemia Group (CALGB 9583) reported on results of a phase III trial using upfront anti-androgen withdrawal alone compared to concomitant use of ketoconazole in 260 patients [22]. This study showed better PSA and objective response in patients who had upfront anti-androgen withdrawal and ketoconazole use compared to those who underwent anti-androgen withdrawal alone, at 27% vs. 11% and 20% vs. 2 %, respectively, though survival was no different. The use of ketoconazole in prostate cancer was explored when this anti-mycotic agent was shown to result in gynecomastia as an adverse effect and further studies showed decline in the testicular and adrenal androgen production [23,24]. Ketoconazole primarily inhibits several cytochrome P450 enzyme family members, including CYP17 [25]. Despite the encouraging results of ketoconazole, this agent's non-specific, unselective enzyme inhibition brings about side-effects which lead to intolerance and discontinuation in many patients. Attempts to improve upon the side-effects and efficacy were therefore undertaken.

b. CYP17 inhibition

Abiraterone acetate is an oral, selective, steroidal inhibitor of cytochrome P450 (17α-hydroxylase and C17,20-lyase activity), an androgen biosynthesis inhibitor [26]. An initial pre-clinical study compared this compound to ketoconazole and was found to significantly reduce ventral prostatic, testicular, and kidney masses and testosterone levels in mice, with evidence of 17α-hydroxylase inhibition [27]. Further clinical studies elucidated the activity

and biologic rationale for the use of abiraterone acetate in castrate-resistant prostate cancer [28,29]. Abiraterone inhibits 17 hydroxylase which results in lowering of serum cortisol, causing an increase in adrenocorticotropic hormone (ACTH). ACTH in turn, brings about an increase in deoxycorticosterone which is responsible for the observed side-effects of secondary mineralocorticoid syndrome and hyperaldosteronism [30]. The initial phase I clinical trial of abiraterone acetate that enrolled 54 patients with a phase II expansion of 42 patients at a 1,000 mg dose, demonstrated PSA declines of greater than 50% in 67% of patients with chemotherapy naïve CRPC and a median time to progression of 225 days [31,32]. One interesting finding in this study is that addition of dexamethasone brought about additional responses in about a third of patients, regardless of prior treatment with dexamethasone, with additional PSA responses of > 50% [32]. The observed benefit with the addition of dexamethasone could be secondary to suppression of hormones upstream of CYP17 that are increased as a result of higher ACTH levels from the use of abiraterone. These hormones upstream of CYP17 may be responsible for promiscuous activation of the AR [32]. Encouraging responses are seen not only in chemotherapy-naïve patients but also in docetaxel-treated and refractory patients as seen in a phase II study with 47 patients. Declines in PSA of ≥30%, ≥50% and ≥90% were seen in 68% (32 of 47), 51% (24 of 47), and 15% (seven of 47) of patients, respectively [30]. In addition, nearly half of patients who had received prior ketoconazole also exhibited PSA declines in 12 weeks [33]. Given these promising results, a phase III study that enrolled 1,180 patients in a multi-center, double-blind, placebo-controlled trial, of abiraterone acetate in combination with corticosteroids in patients declared docetaxel-failure was launched and completed accrual (COU-AA-301), see Table 1. Abiraterone was used in conjunction with low-dose steroids in order to obviate the adverse effects of hyperaldosteronism observed with the use of abiraterone monotherapy [34]. Results showed an improvement in median overall survival of 14.8 months versus 10.9 months, with a hazard ratio of 0.646, translating to a 36% improvement in median survival and a 35% risk reduction in death [35]. Given these promising results, a pre-chemotherapy trial (COU-AA-302) has completed accrual with anticipated results to determine whether starting earlier prior to chemotherapy, would improve overall survival.

Other novel CYP17 inhibitors are currently undergoing further evaluation. VN/124-1 is a dual CYP17 and AR inhibitor that inhibits the growth and more potent than castration in prostate cancer xenograft tumors in immunodeficient mice [36,37]. Given the steroidal structures of both abiraterone and VN/124-1, strategies to employ non-steroidal inhibitors were undertaken. TAK-700, a novel, non-steroidal 17,20 lyase-specific inhibitor has shown promising results in a phase I/II trial in metastatic CRPC [38]. Twenty-six patients with metastatic CRPC were enrolled at 5 different dose levels ranging from 100 mg to 600 mg twice daily dosing. All patients treated with ≥300 mg had a PSA decline. Twelve of 15 pts (80%) who received TAK-700 ≥300 mg for ≥3 cycles had PSA reductions ≥50% and 4 of 15 (27%) had reductions ≥90%. A phase III trial comparing Orteronel (TAK-700) with prednisone versus placebo with prednisone, in both chemotherapy-naïve and post-docetaxel treatment, are currently ongoing (Table 1).

c. 2nd generation anti-androgens

Given the proposed alteration in the recruitment of AR antagonist to agonist activity of anti-androgens, effort to circumvent this property was investigated. MDV3100 is a second-generation anti-androgen that has been shown to improve upon the effects of bicalutamide since it exhibits more potency, interferes with binding of the androgen to the AR, prevents nuclear translocation, induces apoptic effects on prostate cancer tumors, and prevents co-activator recruitment without agonist activity [39]. A phase I/II study was reported in 140 patients with doses ranging from 30 mg to 600 mg [40]. While safety and tolerability were the primary objectives of this study, secondary effects were seen with declines in PSA of

≥50% seen in 78 (56%) of patients. Additional correlative biomarker response with circulating tumor cells (CTC) showed conversion from unfavorable (≥ 5 CTC / 7.5 ml of blood) to favorable (< 5 CTCs/ 7.5 ml of blood) in 25 (49%) of the 51 patients. Other responses including stable bone disease was seen in 61 (56%) of 109 patients and 13 (22%) of 59 patients with soft tissue disease. An international, multi-center, randomized, placebo-controlled, phase III study has recently finished enrollment with a target accrual goal of 1177 patients to determine whether MDV3100 will detect an overall survival difference in patients with metastatic CRPC who have been treated with prior Docetaxel. A phase III trial looking at a chemotherapy-naïve population is still ongoing (see Table 1).

Conclusions and Future Directions

The promise of novel, non-chemotherapeutic approaches to treating castration-resistant prostate cancer is rapidly evolving. Several decades ago, prostate cancer was considered a relatively chemotherapy-insensitive disease. However, the therapeutic landscape gradually changed with the first chemotherapy drug approval of mitoxantrone in 1996 for quality of life and pain relief, but was truly revolutionized in 2004 when docetaxel was approved, this time for survival data. Since then, a hiatus has prevailed with several alternating promising and disappointing results with various drugs being put forth in advanced phases of clinical trials, until the recent success of Sipuleucel-T and cabazitaxel became known. With the advent of encouraging results seen with the use of 2nd-generation hormonal agents, drug approvals in this arena will likely be in the horizon. However, several challenges exist and need to be addressed in bringing forth these agents. What is the best timing and sequencing for these agents? Who should receive the drug? Is it cost-effective? What would be the best criteria to use for measuring tumor response in the era of vaccines and newer hormonal agents? Furthermore, the definition of docetaxel resistance has to be uniformly adopted. Overall, these data support further investigations into the use of novel hormonal targeted agents. The challenge to the oncologic community lies in appropriate allocation of these drugs for the right clinical features and state of prostate cancer which patients present with to achieve the maximum potential therapeutic benefit.

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Table 1

Selected Novel Androgen Targeting Therapy in Phase III Clinical Trials

Agent	Title	Primary Endpoint	Secondary Endpoint	Trial Status/ Clinical Trials Identifier
Orteronel (TAK-700)	A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-based Therapy	OS	PSA response, Pain response, rPFS	Open/ NCT01193257
Orteronel (TAK-700)	A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel Plus Prednisone With Placebo Plus Prednisone in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer	OS, rPFS	Pain progression, CTC changes, PSA progression	Open/ NCT01193244
Abiraterone (CB7630)	A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer (COU-AA-302)	OS, PFS	PSA & Pain response, CTC changes, rPFS	Closed/ NCT00887198
Abiraterone (CB7630)	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy (COU-AA-301)	OS	PSA & Pain response, CTC changes, rPFS	Closed/ NCT00638690
MDV3100	AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients With Progressive Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy (AFFIRM)	OS	PSA response, Pain response, rPFS	Closed/ NCT00974311
MDV3100	A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy (PREVAIL)	OS,PFS	Time to 1st SRE, Time to initiation of chemotherapy	Open/ NCT01212991

Abbreviations: OS: Overall Survival; PFS: Progression-Free Survival; rPFS: radiographic progression-free survival; SRE: Skeletal related event