REVIEW ARTICLE

Emerging therapies targeting castration-resistant prostate cancer

Ioannis K. Gkialas, Charalampos Fragkoulis

Department of Urology, General Hospital of Athens "G.N.A G.Gennimatas", Athens, Greece

Summary

Purpose: Building on decades of research, the past few years have yielded a near expo-nential increase in treatment modalities for patients with metastatic prostate cancer. Individually, these improvements in overall survival may appear modest, however, nearly all of them have a distinct mechanism of action and the possibility of synergistic effects have yet to be established. The promise of a durable impact on the mortality

from metastatic prostate cancer will likely stem from further elucidation of molecular pathways involved in prostate cancer, as well as defining the optimal sequence of treatment for patients with metastatic prostate cancer.

Key words: abiraterone, castration resistant prostate cancer, enzalutamide, radium 223, sipuleucel-T

Introduction

Prostate adenocarcinoma is the most common malignancy diagnosed in US men and the second leading cause of cancer related deaths with approximately 30,000 men succumbing to the disease in 2014 [1,2]. Primary therapy for localized disease consists of either surgical resection or radiation therapy [3], however, for patients with recurrent or metastatic disease, treatment consists of androgen deprivation therapy through depletion or blockage of circulating androgens [4]. While initially effective, most men eventually develop resistance manifested by either clinical, radiographic or most commonly biochemical progression (increase in prostate-specific antigen [PSA] despite "castrate" levels of testosterone)[5]. The development of castration-resistant prostate cancer (CRPC) signals an inappropriate reactivation of the androgen receptor (AR) axis resulting in growth and proliferation [6]. Further targeting of the AR pathway, through either the disruption of adrenal production of androgens with abiraterone acetate [7,8], or inhibition of ligand binding using the second generation antiandrogen enzalu-

tamide, results in increased survival for this population of men [9].

The greatest opportunity for curing prostate cancer occurs when a patient presents with early stage localized disease. Unfortunately, 10-20% of prostate cancer patients present with metastatic disease, and up to one-third of patients who present at an earlier stage will have disease recurrence despite surgical or radiotherapeutic treatment [10]. In over 80% of men with metastatic disease, primary androgen ablation leads to initial clinical improvement and reduction of serum PSA levels. However, almost all advanced metastatic cancers initially treated with androgen ablation will develop into CRPC, the major cause of morbidity and mortality among these men (Table 1).

The first of these new modalities approved for metastatic (m)CRPC was sipuleucel-T autologous immunotherapy. Since its 2010 approval, there have been other agents with differing modes of action that have demonstrated increased survival in the setting of mCRPC. These include the hormonal agents abiraterone acetate and enzaluta-

Table 1. Definition of CRPC. EAU Guidelines 2015 edition

Castrate serum testosterone <50 ng/dL or 1.7 nmol/L plus either:

Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, with PSA >2 ng/dL or

Radiological progression: The appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

Symptomatic progression alone must be questioned and is not sufficient to diagnose CRPC

CRPC: Castration-resistant prostate cancer

mide, the chemotherapeutic agent cabazitaxel, and bone targeting agents such as the radioactive radium 223 dichloride [11,12]. Both abiraterone and enzalutamide are increasingly being used in chemotherapy-naive mCRPC patients on the basis of positive data from the COU-AA-302 (abiraterone) and PREVAIL (enzalutamide) phase 3 studies [13,14].

Chemotherapy

From 2004 until 2010 only docetaxel was approved for "androgen-independent (hormone-refractory) metastatic prostate cancer", now referred to as mCRPC. Historically, chemotherapy using docetaxel plus prednisone was the only therapy to demonstrate a survival advantage in advanced prostate cancer, making it the "gold standard therapy" in this disease state. Cabazitaxel was established as a second line chemotherapy option in patients where primary treatment with docetaxel failed.

Mechanisms of hormone resistance

Hormone-resistant prostate cancer cells actually have an increased number of ARs on their membrane surface and are still sensitive to stimulation and growth by androgenic hormone. In addition there is evidence that prostate cancer cells themselves have the capacity to synthesize androgen and stimulate their own growth. The efficacy of androgen deprivation therapy (ADT) is routinely based on achieving castrate levels of serum testosterone, arbitrarily defined as T ≤20 or 50 ng/dL. However, tissue androgen measurements in men with either locally recurrent or mCRPC clearly demonstrate that prostate and tumor androgen concentrations remain well within the range capable to activate the AR [15,16].

The critical enzyme required for androgen synthesis from cholesterol is cytochrome P450 17 alpha-hydroxylase (CYP17A). Adrenal expression of this enzyme accounts for production of circulating adrenal androgens, including dehydroepi-

androsterone (DHEA, which primarily circulates in its sulfated form, DHEA-S), and androstenedione (AED), and a number of studies [11,13] have demonstrated expression of CYP17A in castration-resistant prostate tumors.

Abiraterone

CYP17A is a single enzyme that catalyzes the sequential hydroxylase (required for cortisol synthesis) and lyase (required for adrenal androgen synthesis) steps that are required for conversion of C21 pregnenolone and progesterone precursors to the C19 adrenal androgens, DHEA and AED. Abiraterone acetate, an orally administered, rationally designed small molecule derived from the structure of pregnenolone, irreversibly inhibits both the hydroxylase and lyase activity of CYP17A with approximately 10-fold greater potency than ketoconazole. Because adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis, abiraterone is coadministered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis [17](Figure 1).

A number of phase I and II studies [7] initially demonstrated that abiraterone suppresses serum androgen levels and achieves PSA and clinical responses in chemotherapy naïve and docetaxel-treated CRPC patients. Phase III studies in chemotherapy naïve (COU-AA-302) [14] and post-docetaxel treated men (COU-AA-301) [18,19] have confirmed these findings, resulting in FDA approval of abiraterone for men with mCRPC either before or after treatment with chemotherapy.

In the post chemotherapy study (COU-AA-301,1195 men) the first interim analysis demonstrated a 3.9 month overall survival benefit for men receiving abiraterone, prompting the independent data monitoring committee (IDMC) to recommend the study be unblinded and men on the placebo arm be offered abiraterone [18]. All secondary endpoints were statistically significant
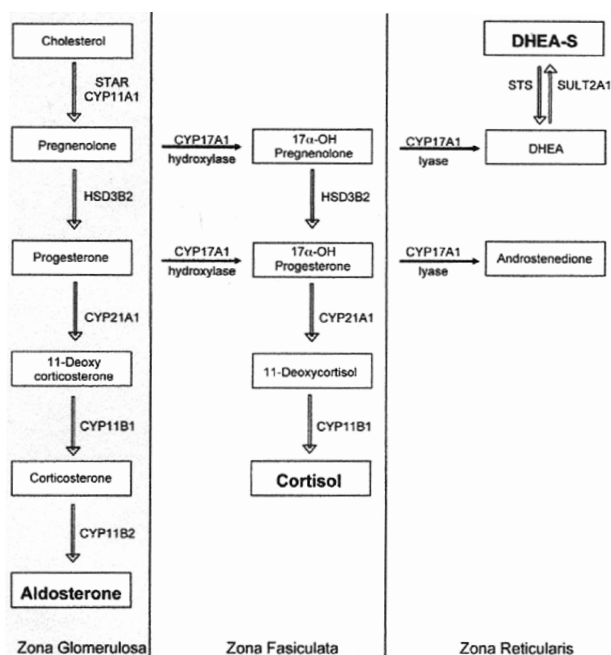
Figure 1. Steroid hormone pathways in the adrenal gland.

in favor of abiraterone, including median time to PSA progression (8.5 vs 6.6 months), median radiologic progression-free survival (rPFS, 5.6 vs 3.6 months), and proportion of patients with >50% PSA response (29.5 vs 5.5%) [19].

In the prechemotherapy study (COU-AA-302,1088 men), at a median follow up of 22.2 months abiraterone doubled rPFS from 8.3 to 16.5 months (HR 0.53, p<0.001), accompanied by a trend for increased overall survival from 27.3 months in the placebo arm to not-reached in the abiraterone group (HR 0.75, p=0.01 which did not meet the prespecified p value of 0.001), again prompting the IDMC to recommend the study be unblinded and men on the placebo arm be offered abiraterone [14]. All secondary end-points were statistically significant in favor of abiraterone, including median time to opiate use (not-reached vs 23.7 months), time to initiation of chemotherapy (25.2 vs 16.8 months), time to performance status decline (12.3 vs 10.9 months), time to PSA progression (11.1 vs 5.6 months), and proportion of patients with > 50% PSA response (62 vs 24%) [14].

Abiraterone is generally well tolerated, with 13% and 19% of abiraterone-treated patients in COU-AA-301 and COU-AA-302 (respectively) discontinuing therapy for adverse effects vs 18% and 23% of placebo-treated patients. The most common adverse events in both groups were fatigue, back pain, nausea, constipation, bone pain and ar-

thralgia, all in the range of 25-30%.

While clinical responses to abiraterone have been remarkable, not all patients respond and the majority ultimately progress with a rising PSA indicating reactivation of AR signaling [20]. Interestingly, recent case reports describe instances of an 'abiraterone withdrawal syndrome,' in which (generally transient) PSA declines occur following discontinuation of abiraterone, suggesting that mutations in the AR which can allow AR activation by exogenous corticosteroids may play a role [21,22]. Numerous studies evaluating the sequencing and combination of abiraterone with immunotherapy, chemotherapy and other AR targeted agents in multiple disease settings are underway.

Enzalutamide

Enzalutamide is an oral potent inhibitor of the AR signaling pathway, with actions including inhibition of ligand/receptor binding, nuclear translocation of activated AR, and inhibition of AR-regulated nuclear transcription [23].

In an early trial, enzalutamide demonstrated antitumor effects irrespective of chemotherapy status [25]. In the subsequent phase III AFFIRM trial [11], enzalutamide significantly prolonged the survival of men with mCRPC after docetaxel chemotherapy and showed favorable results for all secondary endpoints [24]. More recently, enzalutamide significantly improved overall survival in men with chemotherapy-naïve mCRPC in the phase III, PREVAIL trial [24].

The international randomized phase III AFFIRM trial was conducted in 15 countries at 156 sites [11]. A total of 1199 patients with progressive mCRPC were randomized in a 2:1 ratio to enzalutamide 160 mg daily (N=800) or placebo (N=399). A planned interim analysis demonstrated a significant improvement in the primary endpoint of overall survival. Median overall survival was 18.4 months among patients receiving enzalutamide and 13.6 months among patients receiving placebo, an incremental benefit of 4.8 months. The hazard ratio for death was 0.63 (p<0.001), indicating there was a 37% decrease in the risk of death compared with placebo. The superiority of enzalutamide over placebo was further shown for all secondary endpoints, including the time to PSA progression (8.3 vs 3.0 months; hazard ratio 0.25; p<0.001) and rPFS (8.3 vs 2.9 months; hazard ratio 0.40; p<0.001).

The PREVAIL study was a multinational, doubleblind, randomized, placebo-controlled, phase

3 trial of enzalutamide. A total of 1717 patients were enrolled in the study, with 872 in the enzalutamide group and 845 in the placebo group. Coprimary endpoints were radiographic progression-free survival and overall survival. Secondary endpoints included the time until the initiation of cytotoxic chemotherapy, the time until the first skeletal-related event, the best overall soft-tissue response, the time until PSA progression, and a decline in the PSA level of 50% or more from baseline [25]. In the PREVAIL study that involved patients with metastatic prostate cancer who had not received previous chemotherapy, enzalutamide extended the time until radiographic progression or death, improved overall survival, and delayed the initiation of chemotherapy by a median of 17 months. The benefit of enzalutamide on radiographic progression-free survival was observed from the first assessment, 2 months after randomization and conferred a relative reduction of 81% in the risk of progression or death. Enzalutamide significantly reduced the risk of death by 29% over placebo, even though patients in the placebo group had received effective post-progression therapy more frequently and earlier than those in the enzalutamide group. The benefit of enzalutamide was observed as early as 4 months after randomization and was maintained throughout the study [24].

Overall, enzalutamide 160 mg orally daily was well tolerated by patients compared with the placebo control. Although the period of observation for the enzalutamide arm was more than twice that for the placebo group, the rates of adverse effects were similar in the two treatment arms. Overall there was a higher incidence of all grades of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache in the enzalutamide arm compared with placebo. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo [25,26].

Principles of cancer immunotherapy

Cancer is considered an immunosuppressive state that requires an intervention to boost adaptive immunity, including the antigen-specific defense mechanism. One of the key characteristics of cancer pathogenesis is the ability of the tumor cell to avoid immune destruction [27]. Active immunotherapy often referred to as "vaccine therapy" is designed to elicit a host immune response that specifically targets the tumor cell through a T-cell response cascade. Active immunotherapy requires the target antigen to be processed in a

manner capable of inducing an immune response that generates antitumor activity. T-cells do not respond to soluble or naked protein antigens but rather require peptide fragments from the antigen to be "presented" to them on the surface of antigen-presenting cells (APCs) via human leukocyte antigen (HLA) molecules.

Prostate cancer as a target for immunotherapy

Training the host immune system to reject its own developing tumor has been a long unrealized dream. A variety of strategies were attempted in the past to stimulate an immune response in the prostate but none proved successful [28].

The prostate is a highly differentiated, genderspecific organ and prostate adenocarcinoma offers a variety of suitable antigen targets for cancer immunotherapy [29]. Many genes within the prostate are transcriptionally regulated by the AR and show highly regulated expression mostly restricted to the prostate gland or prostate cancer tissue. Included among such expressed genes are PSA, prostatic acid phosphatase (PAP), prostate-specific membrane antigen (PSMA), and prostate stem-cell antigen (PSCA).

Development of sipuleucel-T

Sipuleucel-T represents the first "personalized" immunotherapy for the treatment of cancer using a patient's own immune cells to overcome the self-tolerance hurdle for the treatment of tumors. It is also important to stress that sipuleucel-T is not a gene therapy, since APCs are loaded with a purified recombinant protein and are not genetically manipulated or transfected with any form of viral or recombinant DNA or RNA. Prostatic acid phosphatase was chosen as the target antigen for the prostate cancer treatment because it is expressed at detectable levels in more than 95% of prostate adenocarcinomas and is highly specific to prostate tissue [30-32].

Clinical evidence for immunotherapy with sipuleucel-T

Two early phase III randomized, double-blind, placebo-controlled trials with sipuleucel-T, (trials D9901 and D9902A) comparing sipuleucel-T to placebo in men with asymptomatic, mCRPC demonstrated significantly prolonged survival [34]. However, these small initial trials were combined for an FDA filing which led to the need to

Table 2. Common adverse events reported in the IMPACT trial (≥25% incidence)

Event	Sipuleucel-T (N=338)		Placebo (N=168)	
	All Grades	Grade 3-5	All Grades	Grade 3-5
	N (%)	N (%)	N (%)	N (%)
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills	183 (54.1)	4 (1.2)	21 (12.5)	0
Fatigue	132 (39.1)	4 (1.2)	64 (38.1)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0

Table 3. PSA quartile data from the IMPACT study demonstrating improved survival with lower baseline PSA levels

	Baseline PSA (ng/mL), N = 128			
	≤ 22.1	> 22.1 – 50.1	> 50.1 – 134.1	> 134.1
Median overall survival (months)				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	13.0	7.1	5.4	2.8
Hazard ratio	0.51	0.74	0.81	0.84
95% CI	0.31, 0.85	0.47, 1.17	0.52, 1.24	0.55, 1.29

Table 4. Physical characteristics of radiopharmaceuticals used in prostate cancer

Radionuclide	Half – life (days)	Decay particle	Tissue penetration(mm)
Radium 223	11.8	alpha	< 0.1
Strodium 223	50.5	beta	5.5
Samarium 153	1.9	beta, gamma	2.5
Rhenium 186	3.8	beta, gamma	4.5

perform a larger randomized, double-blind, placebo-controlled phase III clinical registration trial known as the IMPACT study (Immunotherapy for Prostate AdenoCarcinoma Treatment). Briefly, in the 512 patient IMPACT study, the median overall survival was 25.8 months for men receiving sipuleucel-T and 21.7 months for patients who were treated with placebo (p=0.03), a survival advantage of 4.1 months, while possessing a relatively benign safety profile. Adverse events seen more often in sipuleucel-T treated patients than in those receiving placebo included chills, fatigue, and pyrexia that were grade 1 or 2 in severity and of short duration (1 or 2 days), resulting in minimal discontinuation of treatment (< 2%) (Table 2).

The use of PSA in the setting of sipuleucel-T requires some clarification. PSA responses may not be observed in patients who have favorable overall survival benefit from sipuleucel-T. In an exploratory analysis of the IMPACT trial, the greatest magnitude of benefit with sipuleucel-T treatment was seen in patients with better baseline prognostic factors, and in particular those with lower baseline PSA values (Table 3).

This suggests that patients with less advanced disease may benefit most from sipuleucel-T treatment. There is no consensus as to when a patient should be reimaged. Combining sipuleucel-T with other agents and further study of the optimum sequencing of immunotherapy will continue for the next few years [34].

Radium 223 dichloride

Prostate cancer frequently metastasizes to the bone primarily within the axial skeleton (vertebral bodies, pelvis, ribs, and skull) but may also occur in the long bones [35]. Radiographically, osseous metastases are most often noted on 99 technetium methylene diphosphonate bone scintigraphy scans. However, newer modalities such as 18 sodium fluoride PET and 18 fluorodeoxyglucose PET are more frequently being utilized, given their increased sensitivity for detection. Clinically, bone metastases encountered in 80-90% of mCRPC patients are the primary cause of morbidity and mortality [36,37]. Bone lesions may cause pain or skeletal-related events such as spinal cord compression, fractures, or hypercalcemia.

The current radiopharmaceutical agents used against metastatic prostate cancer include strontium-89, samarium-153, rhenium-186, and radium 223 (Table 4).

Historically, primary outcomes included pain response, decrease in analgesic consumption, and quality of life. Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone-mCRPC [38]. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energy close to the origin of the particle emission. Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an alpha emitter, administered intravenously requires no radiation safety precautions such as particular sleeping arrangements, limited time or specified distance from children or pregnant women. Radium 223, an alpha particle emitter, was originally selected given its half-life (11.4 days) that allowed convenient dosing, safe radon daughter isotope and high skeletal uptake in patients with osteoblastic metastases [38]. Pharmacokinetic studies demonstrated that within 24 hours < 1% of the administered dose remained in circulation and was predominantly eliminated via the gastroin-testinal tract.

Radium 223 was recently approved by the FDA in 2013 for the management of men with mCRPC after the publication of a randomized phase III trial which showed an overall survival benefit [38,39]. The phase III placebo-controlled trial randomized 922 men with symptomatic bone-mCRPC using a 2:1 ratio to receive 6 injections every 4 weeks of either radium 223 (50 kBq/kg) or placebo [38]. Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints the time to first skeletal-related event, time to alkaline phosphatase progression, alkaline-phosphatase response, alkaline-phosphatase normalization, time to PSA progression, safety, and quality of life. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223. In addition, there was significant improvement in median time to SRE (13.6 vs 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm. Adverse events were determined for any man who received > 1 injection in 762 patients. Adverse events were observed in 88% of the radium 223 patients and 94% of placebo-treated patients. Serious adverse events were higher in the placebo group (43 vs 55%) and treatment discontinuation due to adverse events was higher in the placebo group (13 vs 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3 vs 1%, thrombocytopenia 6 vs 2%, anemia 13 vs 13%). Given that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient's oral intake and fluid status is crucial to prevent dehydration.

Radium 223 is the first radiopharmaceutical to provide a prolongation in overall survival in men with castration-resistant prostate cancer. The safety profile of radium 223 is encouraging, in comparison to the β emitters, which may allow for increased dosing (phase I study planned), integration with myelosuppressive chemotherapy (NCT01106352, phase I/IIa study of safety and efficacy of radium 223 with docetaxel in patients with bone metastasis from castration-resistant prostate cancer), or novel AR targeting agents (phase I study planned with enzalutamide and abiraterone acetate).

Conclusion

With the rapid introduction of multiple new agents, the lack of clarity regarding the optimal integration of these drugs into the management paradigm of patients with advanced prostate cancer is unsurprising. Other drugs such as cabozan-

tonib, ipilimumab and custirsen are in late stage evaluation and may in the near term add to the armamentarium and quandary of managing patients with advanced prostate cancer [40-42].

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