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Review article

Utility of novel androgen receptor therapies in the real world: A nuanced approach

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Abstract

Abiraterone and enzalutamide are in widespread clinical use because of their favorable safety and efficacy. Nonetheless, even with newer agents, resistance develops overtime. In this review, we discuss mechanisms of resistance to these newer agents as well as novel therapeutic agents. We also review the literature to help clinicians decide which agent to begin with and when to stop or switch androgen receptor agents. © 2016 Published by Elsevier Inc.

Keywords: Prostate cancer; Novel therapies; Androgen receptor therapies; Resistance mechanisms

1. Introduction

1.1. Current landscape and current treatment options

Over time the selection pressure of androgen deprivation therapy contributes to the emergence of prostate cancer that can proliferate and thrive despite castrate levels of testosterone (conventionally described as <50 ng/dl). Virtually all men treated with androgen deprivation therapy would experience disease progression to the lethal state of castrate-resistant prostate cancer. Although this state was previously termed hormone refractory, it has been discovered that androgen receptor (AR) signaling persists in this setting because of a variety of mechanisms. In fact, amplification of the AR has been detected in 20% to 30% of castration-resistant tumors [1,2].

In keeping with this new understanding, the treatment paradigm of metastatic castration-resistant prostate cancer (mCRPC) has expanded in recent years to include novel hormonal agents such as abiraterone acetate (AA), which targets androgen biosynthesis, as well as enzalutamide, which is a direct antagonist of the AR. Newer agents such as Apalutamide (ARN-509) and ODM-201 also work as next-generation AR antagonists found to inhibit AR nuclear translocation and DNA binding and down-regulate AR transcriptional activity. A distinct agent, Galeterone, may exert combined effects (blocking androgen synthesis and serving as an AR antagonist). Eventually, however, progressive disease and resistance to these agents would develop. Data from phase III trials demonstrate that resistance to abiraterone and enzalutamide typically develops within 11 to 18 months of treatment initiation [3–6]. Understanding the various patterns of resistance and what to do next is therefore becoming increasingly important in the treatment of mCRPC.

2. Clinical considerations

2.1. The agents

Abiraterone is a powerful CYP17A inhibitor that suppresses androgen production. In a phase III trial of men with mCRPC, in the postchemotherapy setting (COU-AA-301), treatment with abiraterone and prednisone, in combination, improved survival compared with prednisone alone (14.8 vs. 10.9 mo, hazard ratio [HR] = 0.65, $P < 0.01$). This study led to its first regulatory approval in 2011 [3]. In a second phase III study in chemotherapy-naive men with mCRPC (COU-AA-302) in which the coprimary end points were radiographic progression-free survival (rPFS) and

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overall survival (OS), abiraterone again was superior to placebo (rPFS = 16.5 mo with abiraterone-prednisone and 8.3 months with prednisone alone, HR = 0.43, 95% CI: 0.35–0.52, $P < 0.001$). The median OS was 35.3 with abiraterone-prednisone vs. 30.1 mo with prednisone alone (HR = 0.79 [95% CI: 0.66–0.95], $P = 0.0151$), but did not reach the prespecified statistical efficacy boundary (α level = 0.0035) [7]. Secondary end points, including risk of decline in Eastern Cooperative Oncology Group performance status, time to the initiation of cytotoxic chemotherapy, and time to opiate use for cancer-related pain all favored the abiraterone arm [4]. In the abiraterone studies, the prednisone control alone led to prostate-specific antigen (PSA) decline of ≥50% in 15% to 25% of patients [3,4].

Enzalutamide is a second generation antiandrogen that binds to the AR, inhibiting nuclear translocation of the AR and AR binding to DNA. Preclinical studies showed that enzalutamide has an 8-fold higher affinity for the AR than bicalutamide [8]. In the AFFIRM trial, 1,199 men with castrate-resistant prostate cancer who had received prior docetaxel-based chemotherapy were randomized to either enzalutamide or placebo. Overall survival was significantly increased with enzalutamide compared with placebo (median = 18.4 vs. 13.6 mo, HR = 0.63, 95% CI: 0.53–0.75, $P < 0.001$) that lead to early unblinding in the study.

The survival benefit was consistent across all subgroups. Enzalutamide was significantly better than placebo in all secondary efficacy end points, including PSA, soft tissue response, time to PSA progression, quality of life response, rPFS, and time to first skeletal-related event [5].

In 2014, PREVAIL, a large multicenter phase III clinical trial, demonstrated the role of enzalutamide in the chemotherapy naïve setting. In this trial, 1,717 men who had not received prior docetaxel chemotherapy were randomly assigned to enzalutamide or placebo and had coprimary end points (OS and PFS). Enzalutamide demonstrated a significant benefit in both end points, with a 30% reduction in the risk of death (HR = 0.70, $P < 0.0001$) and an 81% reduction in the risk of radiographic progression or death (HR = 0.19, $P < 0.0001$) with an rPFS at 12 months of 65% with enzalutamide vs. 14% with placebo. Overall survival was significantly increased with enzalutamide compared with placebo (estimated median: 32.4 vs. 30.2 mo, HR = 0.71, 95% CI: 0.60–0.84, $P < 0.0001$) [6]. Needless to say that the postchemotherapy phase III studies of abiraterone and enzalutamide were placebo-controlled (placebo plus prednisone in the abiraterone study), because there were no agreed upon standard of care known to prolong survival in this disease setting [3,5].

Apalutamide (ARN-509) is a potent second generation AR antagonist chemically similar to enzalutamide. Apalutamide binds AR with 7- to 10-fold greater affinity than bicalutamide in human prostate cancer cells and was more efficacious in mouse models of CRPC than enzalutamide. In contrast to bicalutamide, ARN-509 shows no AR agonist properties [9].

Preliminary results from the phase II study for Apalutamide were reported in 2013. Totally, 47 patients with high-risk (PSA ≥ 8, PSA doubling time < 10 mo), nonmetastatic CRPC were enrolled in this study and 91% of those patients experienced a PSA response (>50% decline in PSA) at 12 weeks with an estimated 88% PFS at 12 months [10]. Ongoing studies of ARN-509 include a phase Ib trial of ARN-509 in combination with AA and prednisone (NCT01792687); a phase III, placebo-controlled trial of ARN-509 in patients with nonmetastatic (M0) CRPC (NCT01946204); and a phase II randomized trial of ARN-509 in patients with biochemically relapsed, hormone-sensitive prostate cancer (NCT01790126).

2.1.1. ODM-201

ODM-201 is a novel AR inhibitor with high-affinity binding to the AR and inhibition of AR nuclear translocation. Nonclinical data have also shown negligible penetrance of ODM-201 through the blood-brain barrier, suggesting a lower risk of seizure [11]. In 2014, results from the phase I/II clinical trial ARADES were published. This trial aimed to evaluate ODM-201 in men with progressive mCRPC in an open-label, multicenter trial with a Phase I dose-escalation stage followed by a randomized phase II extension. The drug was well tolerated and no seizures were noted during this trial, in contrast to other novel AR inhibitors. Antitumor activity, shown by a reduction of at least 50% in PSA, was noted in all doses and all treatment stratification subgroups [12]. The phase III trial for ODM-201 is currently accruing participants (ARAMIS; NCT02200614).

2.1.2. Galeterone

Galeterone is a novel AR-targeting agent with multiple mechanisms of action. It inhibits CYP17 and androgen synthesis like abiraterone antagonizes the AR like enzalutamide and in a novel mechanism, unlike the prior 2 drugs, results in the degradation of the AR [13,14]. In the phase I trial, ARMOR1, 49 men with metastatic and nonmetastatic chemotherapy-naïve CRPC were enrolled. The drug was well tolerated and PSA reductions were seen in most patients. A total of 24 (49%) patients had >30% maximal PSA reductions and 11 patients (22%) demonstrated a >50% PSA reductions [15]. Recently, results of the phase II clinical trial, ARMOR 2 Part1 were reported. In ARMOR 2 Part 1, across all doses, 64% (16/25) achieved a 30% PSA decline and 48% (12/25) achieved a 50% PSA decline [16]. Of significance, ARMOR2 demonstrated a PSA decline among patients with AR C-terminal loss, which suggests activity in patients with AR-V7 variants. This is because AR-V7 variants also encode a truncated AR that lacks the C-terminal ligand-binding domain, but retains the transactivating N-terminal domain. Thus, galeterone is entering phase III trials (ARMOR3-SV, NCT02438007)