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Review Article

Expanding armamentarium in advanced prostate cancer management: are all novel antiandrogens the same?

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ABSTRACT

Prostate cancer (PCa) is the most common cancer in men. Androgen receptor axis plays a crucial role in the carcinogenesis of PCa. The mainstay treatment of prostate cancer is blockage of androgen receptor axis but in a vast majority of patient resistance to androgen deprivation therapy is inevitable. After using enzalutamide, the first new generation anti-androgen (AA), two new generation AA drugs were synthesized. New generation anti-androgen drugs are used especially in castration resistance prostate cancer. But recently, there are new publications regarding using new generation anti-androgens in castration sensitive prostate cancer patients. In this review, we will compare structure, mechanisms of effect and clinical outcomes in phase 3 trials of these new generation AA drugs.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men in accordance with GLOBOCAN 2018[1]. In 2019; 174,650 new cases will be seen and 31,620 patients will die from PCa in US[2] Androgen receptor (AR) is a member of steroid hormone receptor family and the AR axis plays a crucial role in the development of PCa[3]. Androgen deprivation therapy (ADT) is mainstay of treatment for patients with PCa but the development of resistance is inevitable. There are several mechanisms causing this resistance[4]. AR gene amplification, AR mutations, expression of AR splice variants, altered expression of AR coregulators, intratumoral androgen synthesis, and post-translational modifications of AR are the most well-known mechanisms of castration resistance[4]. The first generation antiandrogens (AAs) such as bicalutamide have a partial agonistic effect on the AR, which is associated with its limited efficacy in castration-resistance setting[5]. More recently studies of the new and more potent AA drug have established these novel therapies as new standards of care. The first novel nonsteroidal AA, enzalutamide, was approved in 2012[5]. Thereafter, two new AA drugs, apalutamide and darolutamide, have established their roles in the treatment of nonmetastatic castration-resistance PCa (nmCRPCa)[6,7]. In the metastatic castration-resistance PCa (mCRPCa) setting, enzalutamide has an established role as well[8,9]. In this review, we will compare structure, mechanisms of effect and clinical outcomes in phase III trials of these new generation AA drugs.

2. Structure and mechanisms of the effect

Enzalutamide (formerly MDV3100) is an oral nonsteroidal drug and the first of the novel AA. It is a diaryl thiohydantoin compound[5]. It functions through several mechanisms for AR axis inhibition. It blocks interactions of androgen hormone and receptor, inhibits translocation of AR, binding DNA, and also inhibits coactivator recruitment[10]. Unlike first generation AAs, enzalutamide has no agonistic effect on AR and its affinity to their receptor was five to eight-fold more than bicalutamide in vitro[5,11]. When compared with bicalutamide, enzalutamide significantly improved oncological outcomes [reduced the risk of progression or death by 76% compared with bicalutamide (hazard ratio [HR], 0.24; 95% CI: 0.18 to 0.32; $P < .001$)][12]. The mechanism of action of the novel AAs is shown in Figure 1.

Apalutamide (formerly ARN-509) is the second novel AA, and it is a synthetic diaryl thiohydantoin compound such as enzalutamide. Although it has lower steady-state plasma concentrations, preclinical investigations showed that apalutamide was more effective than enzalutamide[13]. All nonsteroidal AAs bind gamma-aminobutyric acid A receptors, thus seizures occur as an

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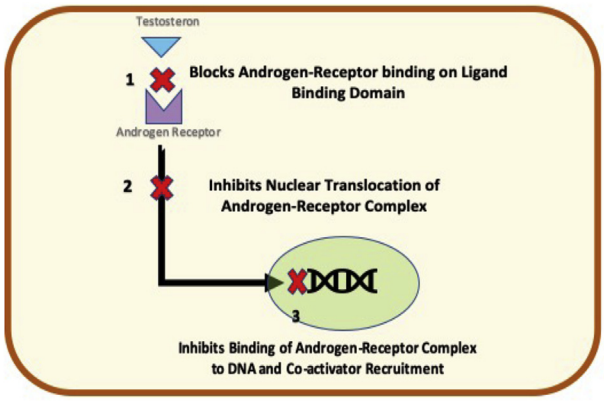

Figure 1. Mechanisms of action of the new generation antiandrogens.

uncommon but severe adverse effect of these agents. However, when compared with enzalutamide, apalutamide has less seizure risk because it has 4-fold lower levels in the brain. In addition, plasma concentrations of apalutamide were lower than enzalutamide but intratumoral concentrations were higher. Plasma free fraction level of apalutamide was higher than enzalutamide because of it is less protein bound[13].

Darolutamide (formerly ODM-201) is the newest novel AA drug. Chemical structure of this agent is different from the other new generation AAs. Its active metabolite is ORM-15341. Darolutamide shows its effect by inhibiting AR similarly to enzalutamide and apalutamide. Darolutamide and its active metabolite have more potent efficacy on AR when compared to enzalutamide and apalutamide[14]. F876 L substitution in AR is remarkable resistance mechanism to AAs and this mutation causes agonistic effect of enzalutamide and apalutamide[14]. However, darolutamide has full antagonistic effect despite mutations of AR. Moreover, in preclinical investigations it is observed that darolutamide and its metabolite have a lower level of brain/plasma ratio than enzalutamide and apalutamide. In addition, unlike enzalutamide, darolutamide does not increase levels of serum testosterone because of effect on hypothalamic-pituitary-gonadal axis[14]. This may contribute to better efficacy of this drug.

3. Landmark phase III trials of novel AAs

Enzalutamide is the first new generation AA drug. The first phase III trial of enzalutamide was the AFFIRM trial. This trial displayed the effect of enzalutamide on patients with mCRPC who were previously treated with docetaxel. There was a risk reduction of death of 37% in patients treated with enzalutamide. There were 5 months difference between groups given enzalutamide or placebo in terms of overall survival (OS) [18.4 months vs 13.6 months (HR: 0.63; 95% CI: 0.53-0.75; $p < 0.001$), respectively], as well. In the enzalutamide group, median radiographic progression-free survival (rPFS) was 8.3 months and median time to first skeletal-related event was 16.7 months (HR: 0.40; 95% CI:0.35-0.47; $p < 0.001$). Compared with placebo, there were more fatigue, diarrhea, musculoskeletal pain, and headache in enzalutamide group and also seizures were 0.6% (5 of the 800 patients) vs 0% of the patients on placebo[9].

A randomized phase III PREVAIL trial showed the effect of enzalutamide on mCRPC before chemotherapy. When compared with the placebo in patients treated with enzalutamide, the risk reduction of death was 29% (HR: 0.71; 95% CI: 0.60-0.84; $p < 0.001$) and median OS was 32.4 months. Median rPFS was not reached in the treatment arm vs 3.9 months in the placebo group. Fatigue was the most common adverse event in enzalutamide group and was similar to that seen in the AFFIRM trial[8]. Hence, enzalutamide was proven as an effective agent for mCRPC both before or after chemotherapy[8,9].

Enzalutamide was approved by the Food and Drug Administration (FDA) in 2012 after the AFFIRM trial for patients with mCRPC who had previously been treated with docetaxel, and in 2014 after the PREVAIL trial for chemotherapy naive patients[15,16]. In 2018, a randomized phase III trial, showed the benefit of enzalutamide in patients with nmCRPCa. In contrast to the AFFIRM and the PREVAIL trials, the primary end point was metastasis-free survival (MFS), which was a new FDA-approved end point for PCa[17]. Median MFS was 36.6 months vs 14.7 months (HR: 0.29; 95% CI: 0.24-0.35; $p < 0.001$) in enzalutamide and placebo groups, respectively[17]. The median time to PSA progression was 37.2 months vs 3.9 months (HR: 0.07; 95% CI: 0.05-0.08; $p < 0.001$) in enzalutamide and placebo groups, respectively[17]. Similar to the AFFIRM and the PREVAIL trials, the most common side effect that has been observed was fatigue and hypertension in the enzalutamide group[17]. There were three patients with seizures in the enzalutamide group, whereas there was none in the placebo group[17]. Although it was observed cyclooxygenase-2 inhibitors reduced PSA velocity in patients with nonmetastatic PCa[18], after the PROSPER trial, enzalutamide was the first agent approved by FDA in 2018 for patients with nmCRPCa[19]. A historical summary for the new-generation NSAAs (enzalutamide, apalutamide, darolutamide) is shown in Figure 2.

Apalutamide is the second approved novel AA in patients with nmCRPCa after the SPARTAN trial[20]. The primary end point of this trial was MFS similar to the PROSPER trial. Median MFS was 40.5 months vs 16.6 months (HR: 0.27; 95% CI: 0.22-0.34; $p < 0.001$) in apalutamide and placebo groups, respectively. The median time to PSA progression was not reached vs 3.7 months (HR: 0.06; 95% CI: 0.05-0.08; $p < 0.001$) in apalutamide and placebo groups, respectively. This trial also showed that after starting treatment for mCRPC, median time until second progression was longer in patients with previously given apalutamide. Recently, interim OS analysis of SPARTAN trial has been announced and it was shown that apalutamide had 25% reduction risk for OS[21]. The most common adverse event was fatigue like enzalutamide. Seizures were seen in two patients in apalutamide group, however there was no patients with seizures in placebo group[6].

The newest novel AA drug for CRPC was darolutamide. Darolutamide has a different structure from the other new generation AAs[14]. The first phase 3 trial of darolutamide was ARAMIS trial in which the effect of darolutamide on patients with nmCRPCa was shown[7]]. The primary end point was MFS like the PROSPER and the SPARTAN trials[7]. The median MFS was 40.4 months vs 18.4 months (HR: 0.4; 95% CI: 0.34-0.50; $p < 0.001$) in darolutamide and placebo groups, respectively[7]. The median MFS was similar in the SPARTAN and the ARAMIS trials and approximately 40 months, however there were 4 months difference in compare with the PROSPER trial (median MFS approximately was 36 months in the PROSPER)[6,7,17]. The median time to PSA progression was 33.2 months vs 7.3 months (HR: 0.13; 95% CI: 0.11-0.16; $p < 0.001$) in darolutamide and placebo groups, respectively[7,17] Clinical outcomes of new AAs in patients with nmCRPCa are shown in Table 1.

The most common side effect noted was fatigue, just similar to enzalutamide and apalutamide[6]. In contrast to the PROSPER and the SPARTAN trials, patients with history of seizures were allowed in the ARAMIS trial[7,14]. There were no differences found between darolutamide and the placebo group in terms of seizures, dizziness, memory impairment and change in mental status[7]. However, the rates of seizure, dizziness and mental impairment disorder were higher in the PROSPER and the SPARTAN trials for enzalutamide and apalutamide, respectively[6,17]. In the ARAMIS trial falls and bone

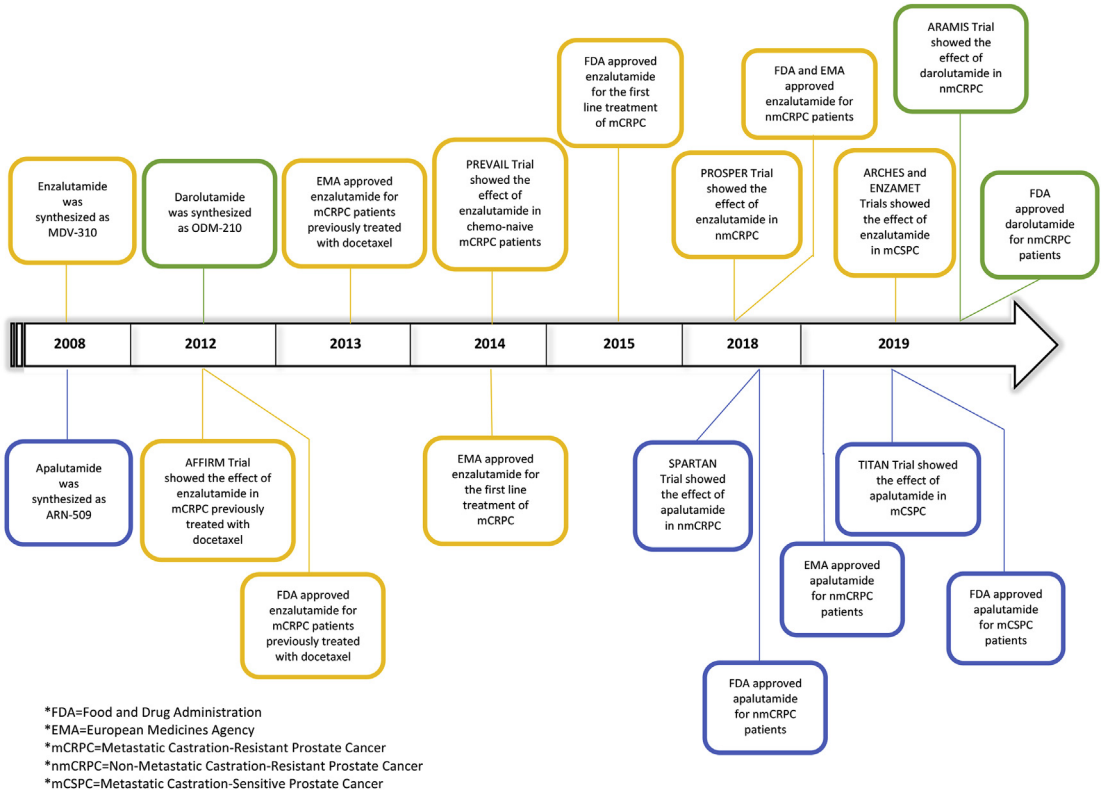

Figure 2. Journey of NSAAs.

fracture risk were similar in darolutamide and placebo groups, however the PROSPER and the SPARTAN trials showed higher falls rates in enzalutamide and apalutamide groups compared with placebo groups[6,7,17]. Hypertension and coronary artery disease were similar in darolutamide and placebo groups, however hypertension was more frequent in enzalutamide and apalutamide groups than placebo groups[6,7,17]. Summary of grade III-IV adverse events of new AAs among patients with CRPCa are shown in Table 2. Furthermore, adverse events leading to discontinuation of the trial regimen were similar in darolutamide and placebo groups but higher in enzalutamide and apalutamide groups compared with placebo groups[6,7,17].

Owing to there were three novel AAs, we had only enzalutamide in the metastatic setting and it was only used in the castration-resistant group. The benefit of enzalutamide and apalutamide has also recently been shown in patients with metastatic castration-sensitive PCa[22,23]. In May 2019, results of the TITAN trial, which showed the effect of apalutamide plus ADT among patients with mCSPC, were published. This study showed, the median rPFS was not reached vs 22.1 months (HR: 0.48; 95% CI, 0.39-0.60; $p < 0.001$) in apalutamide and placebo groups, respectively. The OS at 24 months was 82.4% vs 73.5% (HR: 0.67; 95% CI: 0.51-0.89; $p = 0.005$) in apalutamide and placebo groups, respectively. After subsequent therapy owing to disease progression, the second median PFS was better in the group of patients who were on apalutamide (HR: 0.66; 95% CI: 0.50-0.87). However, subgroup analysis revealed that the effect of apalutamide plus ADT was not seen in patients with mCSPC previously treated with docetaxel and who had low volume disease. The most common side effect was rash in apalutamide group. However, the percentage of fall and seizure were similar in both groups. Furthermore, when compared grade III-IV side effects of apalutamide or placebo treatment, the percentage of patients who had grade III-IV toxicities was similar and it was 42.2% vs 40.8% in apalutamide and placebo groups, respectively. The quality of life was similar in both groups and there was no substantial difference in the Functional Assessment of Cancer

Table 1
Clinical outcomes of the new-generation antiandrogens in nonmetastatic castration-resistance prostate cancer patients

Efficacy endpoints	PROSPER (N = 933)	SPARTAN (N = 806)	ARAMIS (N = 955)
mMFS (months)	36.6	40.5	40.4
HR, (95% CI)	0.29 (0.24-0.35, $p < 0.001$)	0.28 (0.23-0.35, $p < 0.001$)	0.41 (0.34-0.50, $p < 0.001$)
Median time to PSA progression (months)	37.2	NR	33.2
HR, (95% CI)	0.07 (0.05-0.08, $p < 0.001$)	0.06 (0.05-0.08, p*)	0.13 (0.11-0.16, $p < 0.001$)
mOS (months)	NR	NR	NR
HR, (95% CI)	0.80 (0.58-1.09, $p = 0.15$)	0.70 (0.47-1.04, $p = 0.07$)	0.71 (0.50-0.99, $p = 0.045$)
mPFS (months)	N/A*	40.5	36.8
HR, (95% CI)		0.29 (0.24-0.36, $p < 0.001$)	0.38 (0.32-0.45, $p < 0.001$)

mMFS = median metastasis-free survival, mOS = median overall survival, mPFS = median progression-free survival, HR = hazard ratio, CI = confidence interval, PSA = prostate-specific antigen.
*Data not available.

Table 2
Summary of grade III-IV adverse events of the new-generation antiandrogens in Landmark phase III trials among patients with castration-resistance prostate cancer

Grade III or high AE#	Phase III trial						
	AFFIRM (N = 800)	PREVAIL (N = 871)	PROSPER (N = 933)	SPARTAN# (N = 806)	ARAMIS# (N = 955)	TITAN (N = 525)	ENZAMET (N = 563)
Any adverse event (%)	45	43	31	45	24.7	42.2	57.1
Fatigue (%)	6	2	3	0.9	0.4	1.5	6
Back pain (%)	*	3	<1	*	0.4	2.3	1.9
Seizure (%)	<1	<1	<1	0	0	0.2	<1
Mental impairment (%)	*	*	<1	0	0	0	0
Fall (%)	*	1	1	1.7	0.8	0.8	1
Hypertension (%)	*	7	5	14.3	3.1	8.4	8

AE = Adverse event, *Data not available, #Grade III-IV AE in the SPARTAN and ARAMIS trials.

Therapy-Prostate score between apalutamide and placebo groups[22].

In June 2019, the ENZAMET trial, which showed the effect of enzalutamide plus ADT in patients with mCSPC, was published[23]. In contrast to the TITAN trial, enzalutamide plus ADT was compared with nonpotent AA such as bicalutamide, nilutamide or flutamide plus ADT in this trial. The ENZAMET study showed OS was higher in enzalutamide plus ADT group with a percentage at 3 years of 79% vs 72% compared with standard of care (SOC) group[23]. PSA and clinical PFS was better in enzalutamide plus ADT group compared with SOC group. The percentage of PSA PFS at 3 years was 67% vs 37% and the percentage of clinical PFS at 3 years was 68% vs 41% in enzalutamide and SOC groups, respectively. After subsequent therapy due to disease progression, the percentage of patients with progressive disease was lower in the group of patients who had imposed enzalutamide than SOC in the first line setting (67% vs 85% in enzalutamide and SOC groups, respectively). However, there was no difference with respect to OS between enzalutamide and SOC groups among subgroup of patients with high volume disease and visceral metastasis (adjusted p values were 0.14 and 0.33, respectively). The percentage of serious adverse events were 42% vs 34% in enzalutamide and SOC groups, respectively[23]. As expected, seizure was more common in enzalutamide group than SOC group and 7 patients in enzalutamide group had seizure[23]. In the TITAN and the ENZAMET trials, have shown that using novel AAs plus ADT was more effective in terms of OS and PFS than using ADT alone or ADT plus nonpotent AAs in the patients with mCSPC.

4. Conclusion

Our treatment armamentarium for the treatment of advanced PCa has expanded rapidly in the last few years. These agents have not only improved survival but also led to improvements in Quality of life (QOL) for all our patients. However, the lack of phase III comparative studies has made it hard to make decisions on the best therapy or sequence of these novel agents in the respective settings. .Upcoming studies (such as PEACE 1), may help answer some of these questions (NCT01957436)[24] and provide us with important answers on sequencing.

Conflicts of interest

The authors declare no conflict of interest.

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