REVIEW ARTICLE

Update on the Management of Non-Metastatic Castration-Resistant Prostate Cancer

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Abstract

Background: Non-metastatic Castration Resistant Prostate Cancer (nmCRPC) is a heterogenous disease state in which the epidemiology is not completely known. Development of more sensitive modalities for detection of metastasis as well as the emerging data on new generation Androgen Receptor (AR) pathway inhibitors, has changed the paradigm in the management of such patients.

Methods: This is a clinical descriptive review. Using the key words "Non-metastatic castration resistant prostate cancer" and "Androgen receptor targeted agents" in PubMed database, we reviewed and summarized the current literature about the definition, diagnosis and treatment of nmCRPC. We highlight the results of recent Phase III trials that showed significant impact on the outcomes of treatment of nmCRPC. Primary outcome was Metastasis-free Survival (MFS) and secondary outcomes included were Overall Survival (OS) among others as well as rates of Adverse Events (AEs).

Development and Discussion: The SPARTAN trial showed a median MFS for patients treated with apalutamide plus Androgen Deprivation Therapy (ADT) of 40.5 months compared to 16.2 months for patients who received ADT plus placebo [hazard ratio (HR) 0.30; 95% confidence interval (CI) 0.24-0.36; $p < 0.0001$). Apalutamide also showed a statistically significant benefit in OS compared to placebo, with a median of 73.9 versus 59.9 months [HR: 0.78 (95% CI: 0.64-0.96), p: 0.016]. In the PROSPER trial, the median MFS for the enzalutamide group was 36.6 months compared to 14.7 months for the placebo group [HR: 0.29 (95% CI: 0.24-0.35), $p < 0.0001$]. OS was significantly higher in the enzalutamide group (67 versus 56.3 months in the placebo group), reaching the statiscal significance [HR: 0.73 (95% CI: 0.61-0.89), p: 0.001]. The ARAMIS trial showed a median MFS for patients treated with darolutamide plus ADT of 40.4 months compared to 18 months for the placebo group [HR: 0.41; (95% CI: 0.34-0.5); $p<0.001$]. The benefit of darolutamide in OS was also clear, with a HR of 0.69 (95% CI: 0.53-0.88), p: 0.003].

Conclusions: Apalutamide, enzalutamide and darolutamide have demostrated an increase in MFS and OS with a good safety profile in patients with high risk nmCRPC. There are no recommendations in favor of any drug so far, comparative studies are needed.

Keywords: Non-metastatic Castration Resistant Prostate Cancer, Androgen Receptor Targeted Agents, Metastasis-free Survival

INTRODUCTION

Epidemiology of Prostate Cancer

Prostate cancer is the second most diagnosed cancer in men in the world although in Europe and Spain it is in first place (436.500 in Europe in 2012 and 32.641 in Spain in 2014), with an estimated incidence in Spain for 2020 of 35.126 new cases[1].

In many Western countries, the incidence has increased dramatically since the early 1990s due to introduction and generalization of use of the Prostate Specific Antigen (PSA) test[2]. Age has a strong relationship with prostate cancer, with an increase in incidence from age of 50 and it is the main risk factor. The 5-year relative survival of patients diagnosed in the period 2000-2007 was 84.6%, the highest after testicular tumor[3].

Thanks to diffusion of screening programs with PSA, the number of diagnoses in early stages has increased, allowing local treatment with surgery or radiotherapy. However, between 20 and 40% of patients with radical prostatectomy[4] and between 30 and 50% of patients with radiotherapy, present biochemical recurrences after 10 years of follow-up[5]. Patients with recurrences after local therapy or presence of metastatic disease are initially treated with Androgen Deprivation Therapy (ADT). However, there are patients who develop progression in spite of ADT, approximately at 5 years of follow-up. This phenomenon is known as Castration-resistant Prostate Cancer (CRPC)[6].

Definition of CRPC

Castration resistant is defined as presence of serum testosterone level < 50 ng/dL or 1.7 nmol/L plus either biochemical progression: three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or radiological progression: the appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) (Table 1)[7].

Table 1: RECIST 1.1 Definitions of Response Classification

RECIST 1.1 Definitions of Response Classification	
Complete response	Disappearance of all target lesions; any pathologic lymph nodes (whether target or nontarget lesions) must have reduction in short axis to less tan 10 mm.
Parcial response	At least a 30% decrease in the sum of diameters of target lesions; reference the baseline sum diameters.
Progressive disease	At least a 20% increase in the sum of diameters of target lesions; reference is the smallest sum on study (this includes the baseline sum if that is the smallest on study): in addition to the relative increase of 20%, the sum must also demostrate an absolute increase of at least 5 mm; any appearance of one or more new lesions is also considered progression.
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

METHODS

This is a clinical descriptive review. The key words used have been "Non-metastatic castration-resistant prostate cancer" and "Androgen receptor targeted agents". Relevant scientific papers were retrieved from PubMed database and Cochrane Library. The publication language was limited to English and Spanish. Articles searched were limited to the last 15 years.

Of all articles found, those that included words such as "Metastatic castration-resistant prostate cancer" and "Hormone-sensitive prostate cancer" were eliminated. Articles with no available data were also eliminated. Non-clinical controlled trials, editorials, letters to the editor, reviews and meeting abstract were not included.

In addition, the different clinical guidelines of the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have also been reviewed and included in this review.

We highlight the results of recent Phase III trials that showed significant impact on the outcomes of treatment of nmCRPC. Primary outcome was Metastasis-free Survival (MFS) and secondary outcomes included were Overall Survival (OS), time to pain progression, time to cytotoxic chemotherapy, time to first symptomatic skeletal event, progression-free survival, time to PSA progression, time to first prostate cancer-related invasive procedure and time to initiation of subsequent anti-neoplastic therapy. Rate of Adverse Events (AEs) was also analyzed.

DEVELOPMENT AND DISCUSSION

Overview of nmCRPC

The epidemiology of this stage of disease is not completely known[8], however 5-year limited duration prevalence has been estimated around 7% of total prostate cancers in the European Union, according to prevalence model developed by *Liede et al.*[9]. Several series showed a median survival of less than 3 years[10].

Kirby et al. conducted a systematic review in 2011, including 12 studies with a total of 71.179 patients observed for up to 12 years. They concluded that 10-20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up. Two studies reported the prevalence of bone metastases present at diagnosis of CRPC. Together, ≥ 84% were shown to have metastases at diagnosis. Of those patients with no metastases present at diagnosis of CRPC, 33% could expect to develop them within 2 years[11].

Micrometastases are usually undetectable with conventional imaging tests such as Computerized Axial Tomography scan (CT scan) and bone scan[12]. The development of new imaging techniques, such as choline-PET, PSMA-PET or fluoride-PET could change the landscape of this disease in the early diagnosis of micrometastases and therefore in the treatment and prognosis of these patients.

The current consensus established for Prostate Cancer, Radiographic Assessments for Detection of Advanced Recurrence (RADAR I), suggested the need of performing a bone scan and a CT scan when the PSA reached 2 ng/mL; and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every

doubling of the PSA, based on PSA testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level[13].

A retrospective study published in 2019 by *Fendler et al.* included 200 patients with nmCRPC, with PSA values >2 ng/mL and PSA doubling time (PSA-DT) values ≤10 months and/or Gleason ≥8. In this study, 196 patients presented positive PSMA-PET; 44% pelvic disease and 55% metastatic disease despite negative results in conventional imaging tests[14].

Based on these findings, RADAR consensus update for next-generation imaging tests (RADAR III) has been published in 2019. The use of choline-PET, PSMA-PET or fluoride-PET is recommended for patients with PSA-DT values < 6 months when treatment of metastatic disease is considered and when these imaging tests are available[15].

Kinetics of metastatic progression in CRPC

Over the years, several drugs have been studied to delay the appearance of metastasis in patients with CRPC. There are three prospective clinical trials analyzing the development of bone metastases based on bone-targeted pharmacological agents; zoledronic acid, atrasentan; an endothelin A receptor antagonist and denusumab; fully human anti-RANKL monoclonal antibody. Beyond the results obtained in all of them, these data served to elaborate an epidemiological database that allowed to know the risk of metastatic progression in this heterogeneous group of patients.

Smith el al. in 2005, elaborated a randomized, double blind, placebo-controlled clinical trial to evaluate the effects of zoledronic acid on time to first bone metastasis in patients with nmCRPC, defined as elevation of PSA in spite of treatment with ADT. The study stopped early because an intermediate analysis showed that the rate of events observed was lower than expected. Although no evaluation of efficacy could be performed, outcomes from the 201 patients included in the placebo arm were reported to describe the natural history of rising PSA in nmCRPC. The first observation was that the time until the development of the first bone metastasis was 30 months, which was longer than expected. At 2 years, only 33% of the patients had developed bone metastasis. Median time to the first bone metastasis and OS were not achieved. This study suggests that patients with nmCRPC with rising PSA despite ADT have a relatively indolent natural history. Nevertheless, baseline PSA greater than 10 ng/mL and a high PSA velocity, independently predicted shorter time to bone metastasis and overall survival[16].

With this information available, in 2008 *Nelson et al.* developed a placebo controlled clinical trial with atrasentan. The study did not achieve its primary endpoint, showing non-statistically significant difference in time to disease progression. However, the study showed some interesting findings regarding the natural history of nmCRPC. Analyzing the placebo arm, progression was observed in 56.3% of patients. The first metastatic manifestation was skeletal in 44.3% of patients, while only in 8% of patients it was extra skeletal. These data concluded that in nearly 80% of patients, skeleton is the first metastasis location[17].

The third trial, reported in 2012 by *Smith et al.*, investigated the benefit of denosumab in 1432 patients with nmCRPC at high risk of bone metastasis, determined

by PSA > 8ng/mL and/or PSA-DT ≤ 10 months. In this case, denosumab showed a statistically significant prolonged bone metastasis free survival (BMFS) [29.5 months versus 25.2 months in the placebo group, with a Hazard Ratio (HR) of 0.85 and a 95% Confidence Interval (CI), 0.73 to 0.98, p: 0.028] with no difference in OS (HR: 1.01)[18]. Moreover, in an exploratory analysis, they evaluated the relationship between PSA-DT and BMFS. The median BMFS among patients in the placebo group, was 22.4 months in patients with PSADT ≤10 months, 18.7 months in patients with PSA-DT ≤ 6 months, and 18.3 months in patients with PSA-DT ≤ 4 months[19].

These studies pinpoint at three important messages. The first one is that the skeleton is the first metastatic site in CRPC. This provides a strong rationale for developing newer imaging modalities to evaluate the extent of bone metastasis. Secondly, it is suggested that nmCRPC is a heterogeneous disease that overall progresses slowly, with median MFS longer than 2 years. Considering the potential toxic effect of the available bone-targeted pharmacological agents and the fact that they have not shown any benefit in OS, their use is not recommended in these patients. Finally, these results confirmed that the PSA-DT is the most useful parameter to study the risk of metastatic progression and to monitor their progress.

Treatment of nmCRPC

Pathophysiology of Castration-resistant

The common physio-pathological mechanisms for most CRPC is a re-activation of AR transcriptions in a low serum testosterone environment that translates biologically in an elevation of the PSA. Because AR mutations often occur in low testosterone environments, anti-androgen drugs can transform their antagonist activity into agonist. This allows an AR activation in spite of ADT. In patients treated with complete ADT (GnRH agonists and anti-androgens), if anti-androgen drug is interrupted when the patient becomes Castration-resistant, it may suppress the AR activity and induce a PSA response. This phenomenon is known as anti-androgenic withdrawal syndrome[20,21].

Traditional Therapeutic Options

For many years, physicians have tried to modulate the timing and modalities of hormone therapy trying to increase the duration of hormone responsiveness[20]. For this reason, different therapeutic options have been used in modulation of hormone therapy as well as the use of other drugs in management of nmCRPC (Table 2). Although it exists a strong physiological justification for further manipulation in hormone therapy, there are few clinical data and all published studies on these drugs show no clear benefit beyond a modest PSA decrease in the short-term[21].

Other drugs have been used such as adrenal synthesis inhibitors; ketoconazole or aminoglutethimide, estrogens and derivatives as diethylstilbestrol (DES), megestrol or corticosteroids as prednisone, hydrocortisone or dexamethasone. These drugs have not shown enough robust results to be used as therapy in nmCRPC and have therefore been relegated to the background today.

Table 2. Traditional therapeutic options in management of nmCRPC [21].

Traditional therapeutic options	% PSA response (50% decrease)	Duration (months)
Anti-androgens withdrawal syndrome	15-50%	3-6
Anti-androgens	4-50%	3-11
Adrenal synthesis inhibitors	27-63%	4-20
Estrogens	12-81%	2-7
Corticosteriods	14-61%	2-8

Current Therapeutic Options

In 1966, Dr. Huggins was awarded with the Nobel Prize in Medicine for discovering that the AR could be blocked and used as a possible treatment of advanced prostate cancer. The AR is activated by androgenic ligands that allow its dimerization and translocation to the nucleus, activating a transcriptional system that promotes cell survival and proliferation as well as PSA secretion[22]. AR inhibitors are intended to block this process by preventing the nuclear translocation of the receptor and decreasing the cell response.

In recent years and based on pathophysiology of Castration-resistant, new therapeutic targets have been developed for the treatment of nmCRPC, these are AR inhibitors such as enzalutamide, apalutamide and darolutamide.

Enzalutamide is a potent AR ligand-binding domain and signaling inhibitor approved by the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Spanish Agency for drug and Health Products (AEMPS) for the treatment of nmCRPC.

The STRIVE clinical trial published in 2016, is a randomized, double-blind, phase II clinical trial in which CRPC patients were randomly assigned to receive bicalutamide or enzalutamide. Patients with and without metastatic disease were included. The primary outcome was progression-free survival (PFS), including PSA or radiographic progression. Enzalutamide significantly reduced the risk of progression or death [HR: 0.24 (95% CI: 0.18-0.32), $p < 0.001$]. The effect was consistent across all prespecified subgroups, including disease state (non-metastatic vs metastatic). In the subgroup of non-metastatic patients median PFS was not reached with enzalutamide, compared to 8.6 months with bicalutamide [HR: 0.24 (95% CI: 0.14-0.42)][23].

Thanks to these preliminary beneficial results for the use of enzalutamide in patients with nmCRPC, PROSPER, a new phase III, double blind, placebo-controlled and randomized clinical trial was designed. The trial included 1.401 patients with nmCRPC, PSA-DT $\leq$ 10 months and PSA $\geq$ 2 ng/ml. They were randomly assigned in a 2:1 ratio to receive enzalutamide at a dose of 160 mg once daily (N: 933) or placebo (N: 468), while continuing ADT. Patients were stratified according to PSA-DT (< 6 months or $\geq$ 6 months) and the use of bone-targeted drugs (yes or no)[24].

Both demographics and baseline characteristics were similar in both treatment groups. Median age was 74 years-old in the enzalutamide group and 73 years old in the placebo group. Median PSA-DT was 3.8 months in the enzalutamide group

and 3.6 months in the placebo group. Seventy one percent of patients were caucasian, 16% were asian, and 2% were black. Eighty one percent of patients had an ECOG functional status score of 0 and 19% of 1. Metastasis-free survival (MSF) was the primary outcome, defined as the time from randomization to radiographic progression or death from any cause without evidence of radiographic progression, whichever occurred first. Secondary endpoints evaluated were time to PSA progression, time to first use of subsequent antineoplastic therapy, quality-of-life assessments, OS and safety[24].

Enzalutamide resulted in a 71% lower risk of radiographic progression or death than placebo [HR: 0.29 (95% CI: 0.24-0.35), p < 0.0001]. The median MFS was 36.6 months (95% CI: 33.1-not reached) in the enzalutamide group versus 14.7 months (95% CI: 14.2-15) in the placebo group, with a median follow-up of 18.5 months and 15.1 months, respectively. The MFS benefit was consistent in all patient subgroups, including PSA-DT (< 6 months or ≥ 6 months), demographic region (North America, Europe, rest of the world), age (< 75 or ≥ 75) and previous use of a bone-targeted drug (yes or no). Enzalutamide resulted in a 93% lower risk of PSA progression than placebo [HR: 0.07 (95% CI: 0.05-0.08), p < 0.0001]. The median time to PSA progression was 37.2 months (95% CI: 33.1-unreached) in the enzalutamide group versus 3.9 months (95% CI: 3.8-4) in the placebo group. Delay in time to first use of new antineoplastic therapy was greater with enzalutamide than with placebo [HR: 0.21 (95% CI: 0.17-0.26), p < 0.0001]. The median time to first use of new antineoplastic therapy was 39.6 months (95% CI: 37.7-unreached) in the enzalutamide group versus 17.7 months (95% CI: 16.2-19.7) in the placebo group[24].

The median reporting period for adverse events was 18 months in the enzalutamide group and 11.1 months in the placebo group. Adverse events of grade 3 or higher were reported in a higher percentage of patients in the enzalutamide group than in the placebo group. The most common was fatigue. Adverse events of special interest that occurred more frequently in the enzalutamide group than in the placebo group were hypertension (in 12% vs. 5%), major adverse cardiovascular events (in 5% vs. 3%), mental impairment disorders (in 5% vs. 2%) and falls with non-pathological fractures (in 17% vs. 8%).

At the first interim analysis, all primary and secondary endpoints met the criteria for significance except for OS, which had not reached the median in either arm. Therefore, the analysis was considered final for all these endpoints, and the trial was unblinded. Patients in the placebo group were given the opportunity to receive enzalutamide (87 patients in the placebo group received enzalutamide). Based on this study, enzalutamide was approved by the FDA in 2018 and the EMA in 2019 for patients with high risk nmCRPC.

The final analysis showed a statistically significant benefit in OS [HR: 0.73 (95% CI: 0.61-0.89), p: 0.001]. The median OS was 67 months in the enzalutamide group compared to 56.3 months in the placebo group. With a median treatment duration of 33.9 months in the enzalutamide group and 14.2 months in the placebo group, the adverse events were consistent with the ones reported earlier. When adjusting by exposure, there were no differences in the rate of adverse events grade 3 or higher (17 per 100 patient-years in the enzalutamide group vs 20 per 100 patient-year in the placebo group)[25].

Apalutamide binds directly to the

ligand-binding domain of the AR. This drug was approved by the FDA and the EMA for the treatment of nmCRPC high risk patients. In a phase 2 study involving men with nmCRPC who were at high risk for disease progression (with a PSA level of ≥8 ng/mL or PSA-DT ≤10 months), apalutamide resulted in durable PSA responses[26].

Thanks to these beneficial results in favor of the use of apalutamide in nmCRPC, a phase III clinical trial known as SPARTAN was developed. It was a randomized, double-blind, placebo-controlled clinical trial that concluded that the use of this antiandrogen in high risk nmCRPC improves MFS[27].

The trial included 1.207 patients with high risk nmCRPC (PSA-DT ≤ 10 months). They were randomly assigned in a 2:1 ratio to receive apalutamide (240 mg once daily) or placebo, while continuing ADT. The median age was 74 years old. The racial distribution was 66% caucasian, 5.6% black and 12% asian. In both treatment groups, 77% of patients had previously received surgery or radiation therapy as local treatment, 81% had a Gleason score of 7 or more and 15% had pelvic lymph nodes.

MFS was the primary end point. The analysis for MFS was performed after distant metastasis or death had been observed in 378 patients: 184 (22.8%) in the apalutamide group and 194 (48.4%) in the placebo group. The median MFS was 40.5 months in the apalutamide group compared with 16.2 months in the placebo group (HR: 0.30; 95% CI: 0.24-0.36; p < 0.0001).

Apalutamide also demonstrated significant improvement in secondary end points such as median time to metastasis (HR: 0.28; 95% CI: 0.23-0.34; p < 0.0001), median progression-free survival (HR: 0.30; 95% CI: 0.25-0.36; p < 0. 0001) and median time to symptomatic progression (HR: 0.45; 95% CI: 0.32-0.63; p < 0.0001). The first interim analysis of OS showed favorable results although not statistically significant (HR: 0.70; 95% CI: 0.47-1.04; p: 0.0742).

The trial regimen was discontinued owing to progressive disease in 155 patients (19.3%) in the apalutamide group and in 210 (52.8%) in the placebo group. Adverse events led to discontinuation of the trial regimen in 85 patients (10.6%) in the apalutamide group and in 28 (7%) in the placebo group. The rate of serious adverse effects was similar in both groups (24.8% in the apalutamide group vs. 23.1% in the placebo group), assuming 10 deaths vs. 1, respectively. The most frequent adverse effects were fatigue (30.4% vs. 21.1%), skin rash (23.8% vs. 5.5%), falls (15.6% vs. 9%), fractures (11.7% vs. 6.5%), hypothyroidism (8.1% vs. 2%) and seizures (0.2% vs. 0%)[28].

Since the primary endpoint was met at the first analysis, apalutamide was approved by the FDA in the EMA in 2019 and the study was unblinded. Therefore, 76 patients in the placebo group received apalutamide (19%). In the final OS analysis, with a median follow-up of 52 months, median OS in the apalutamide group was significantly longer than in the placebo group (73.9 vs 59.9 months), reaching the prespecified statistical significance [HR: 0.78 (95% CI: 0.64-0.96), p: 0.016][29].

Several articles have been published comparing the efficacy of enzalutamide and apalutamide in the treatment of high risk nmCRPC.

The first of them, published by *Wallis et al.* in 2018, did not find statistically significant difference between both treatments and concluded that they had a similar efficacy in delaying the onset of metastasis[30].

Another more recent article, published in 2020 by *Chowdhury et al.* concluded, however, that apalutamide may provide benefit compared with enzalutamide in nmCRPC in terms of MFS and OS with a probability of 74% and 83% respectively. The authors justify that these disparate conclusions between the two articles could be related to the type of statistical analysis used, although they recommend further analysis to reach strong conclusions[31].

The last AR antagonist studied and approved by the FDA and the EMA in 2020 for the treatment of nmCRPC was darolutamide. It is a third-generation drug with a distinct structure that offers a potential for fewer and less severe toxic effects than apalutamide and enzalutamide because of its low penetration of the blood–brain barrier and low binding affinity for γ-aminobutyric acid type A receptors. This safety profile was objectified in the phase I and II study, known as ARADES and published in 2014[32].

The phase III clinical trial known as ARAMIS was published in 2019, and it concluded that darolutamide is an effective and safe drug in the treatment of high risk nmCRPC[30]. It was a double-blind, placebo-controlled and randomized clinical trial. A total of 1509 patients with PSA-DT ≤ 10 months were randomly assigned in a 2:1 ratio to receive either darolutamide (600 mg given as two 300-mg tablets) twice daily with food (a daily dose of 1200 mg) (64%) or matched placebo (36%) while continuing ADT.

The median age of the patients was 74 years-old and the median follow-up was 17.9 months. Twenty one percent of patients presented lymph nodes in imaging tests and all of them had an ECOG performance status of 0 or 1.

The primary end point was MFS which was 40.4 months in the darolutamide group, as compared with 18.4 months in the placebo group [HR: 0.41; (95% CI: 0.34-0.5); p<0.001]. In the first interim analysis of OS with 136 deaths, darolutamide group presented a lower risk of death than the placebo group, although it did not show statistically significant results, as the other androgenic antagonists [HR: 0.71; (95% CI: 0.5-0.99); p: 0.045].

Other secondary end points such as time to pain progression, time to use of cytostatic chemotherapy, time to first symptomatic skeletal event, or time to PSA progression were significantly higher in the darolutamide group than the placebo group.

In the darolutamide group, 83.2% of patients reported adverse effects compared to 76.9% in the placebo group. The majority were grade 1 or 2 (54.6% in the darolutamide group and 54.2% in the placebo group) and grade 5 were similar in both groups (3.9% and 3.2% respectively). The incidence of adverse events was similar in both groups with the exception of fatigue, which was higher in the darolutamide group than placebo group (12.5% vs. 9.6%).

The incidence of falls or fractures was higher in the darolutamide group than the placebo group, as well as seizures, skin rash or hypothyroidism. There was not an increase of hypertension or alterations of the Central Nervous System[33].

After the results from the first interim analysis were published, the study was unblinded, and the 170 patients that remained in the placebo group crossed over to receive darolutamide. With a median follow-up of 29 months, darolutamide showed a statistically significant benefit in

OS with 83% of patients alive at 3 years in the darolutamide group compared to 77% in the placebo group [HR: 0.69 (95% CI: 0.53-0.88), p: 0.003][34].

A meta-analysis published in 2019 on the use of new hormonal agents in the treatment of nmCRPC, which included the aggregated data from the interim analyses of the three phase III randomized trials mentioned above (PROPSER, SPARTAN and ARAMIS), concluded that these drugs improve MFS with statistically significant differences [HR: 0. 32; (95% CI: 0.25-0.41); p < 0.001; I 2: 77.55%; p: 0.011]. The data on OS was still immature when this study was published.

The administration of these hormonal agents was significantly associated with increased risk of treatment-related death [Relative Risk (RR): 2.41; (95% CI: 1.37-4.24); p: 0. 002]: cardiovascular events [RR: 2.44; (95% CI: 1.39-4.28)], fractures [RR: 2.24; (95% CI: 1.03-4.86)], falls [RR: 2; (95% CI: 1.01-4.06)], and hypertension [RR: 1.38; (95% CI: 1.06-1.8)]. The risk of fatigue, diarrhea, skin rash or seizures did not increase. However, enzalutamide was associated with increased risk of death and fatigue and apalutamide with increased risk of falls, fractures and skin rash, while darolutamide increased risk of cardiovascular toxicity (similar to enzalutamide)[35].

Current Recommendations

Thanks to development and study of new AR targeted agents in recent years and their subsequent approval by the FDA and the EMA, different societies such as EAU and NCCN recommend their use for patients with high risk nmCRPC (PSA-DT ≤ 10 months) with a strong evidence rating, always in combination with ADT.

The three drugs studied (enzalutamide, apalutamide and darolutamide) have the same recommendation because all of them have shown benefit in MFS, OS and all other secondary endpoints with no significant safety issues, and there is no randomized trial comparing the three drugs[36,37].

CONCLUSIONS

Non-metastatic castration-resistant prostate cancer includes a heterogeneous group of patients. It is essential to follow up with PSA values and imaging tests (CT scan and bone scan). Currently, new diagnostic techniques such as choline-PET, PSMA-PET or fluoride-PET are even being recommended in patients with PSA-DT < 6 months because it has demonstrated that this value is a key prognostic factor in the development of metastasis.

Over the years, several pharmacological therapies have been studied to delay the appearance of metastatic disease as modulation of hormone therapy and other drugs. However, none of them showed good results.

Thanks to the development of the new AR targeted agents such as enzalutamide, apalutamide and darolutamide, it has been possible to increase MFS and OS with a good safety profile in patients with high risk nmCRPC. All of them have a strong evidence rating in different therapeutic guidelines and it is an important advance in management of these patients. For these reasons, future comparative studies are needed.

CONFLICTS OF INTEREST

The authors of this article do not have any conflict of interest.

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