Non-Metastatic Castration-Resistant Prostate Cancer

Subjects: Oncology
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Non-metastatic castration-resistant prostate cancer (nmCRPC) is defined by a progressively rising prostate-specific antigen level, despite a castrate level of testosterone, in the absence of obvious radiologic evidence of metastatic disease on conventional imaging modalities. As a significant proportion of patients with nmCRPC develop metastatic diseases, the therapeutic goals of physicians for these patients are to delay metastasis development, preserve quality of life, and increase overall survival (OS). Since 2018, the treatment of nmCRPC has changed dramatically with the introduction of second-generation androgen receptor inhibitors, such as enzalutamide (ENZA), apalutamide (APA), and darolutamide (DARO).

Keywords: second-generation androgen receptor inhibitors ; non-metastatic castration-resistant prostate cancer ; apalutamide ; enzalutamide ; darolutamide

1. Introduction

To assist in clinical decision making, six index patients were described in the American Urology Association guideline to represent the most common clinical scenarios; the disease condition of the first index patient was defined as asymptomatic, nmCRPC [1]. The National Comprehensive Cancer Network guidelines define nmCRPC as CRPC lacking evidence of metastases on conventional imaging [2]. More specifically, the Prostate Cancer Clinical Trials Working Group 3 defined nmCRPC as a progressively rising prostate-specific antigen (PSA) level, namely a 25% PSA increase from nadir (starting PSA ≥ 1.0 ng/mL), with a minimum increase of 2 ng/mL despite a castrate level of testosterone (<50 ng/dL) in the absence of obvious radiologic evidence of metastatic disease on conventional imaging modalities [3].

A substantial percentage of patients with nmCRPC develop metastatic lesions. Smith et al. reported that 46% of men with nmCRPC developed metastasis within 2 years [4][5]. Recently, Moreira et al. also reported that among nmCRPC patients, nearly 60% developed metastatic disease during the first 5 years, with most of the cases of metastasis occurring within the first 3 years [6]. In nmCRPC, baseline PSA level, PSA velocity, and PSA doubling time (PSADT) have been associated with time to bone metastases, MFS, and OS [7][8][9]. Therefore, the therapeutic goals of physicians in these patients are to delay metastasis development, preserve quality of life (QOL), and increase OS.

2. Comparison of Efficacy and Safety of Second-Generation ARi

Presently, the scope of FDA approval for the three drugs differs. apalutamide (APA) is approved for nmCRPC and metastatic castration-sensitive prostate cancer (mCSPC) [10][11][12][13]. enzalutamide (ENZA) is an androgen receptor antagonist approved for all three indications: nmCRPC, mCSPC, and mCRPC [14][15][16][17]. Finally, darolutamide (DARO) is an androgen receptor antagonist approved only for nmCRPC [18].

These ARi have been proven effective in phase III RCTs in patients with nmCRPC. Many similarities exist among the SPARTAN, PROSPER, and ARAMIS trials. All participants had high-risk nmCRPC, defined by a baseline PSA level of 2 ng/mL and a PSADT ≤10 months, and the primary endpoint in each trial was MFS as assessed by computed tomography and a bone scan of the pelvis, chest, and abdomen every 16 weeks. The three RCTs targeted high-risk patients with nmCRPC. Nodal disease was present in patients in all three trials. Although both the ARAMIS and SPARTAN trials permitted the enrolment of patients with malignant nodes <2 cm in diameter located below the aortic bifurcation, only the SPARTAN trial set a threshold of node size <1.5 cm. All patients underwent ADT throughout the intervention phase.

There was one difference between the participants in the three trials; patients with a history of seizures were excluded from the PROSPER and SPARTAN trials. This is because administration of ENZA or APA is associated with an increased risk of seizures [19][20][21] due to penetration of the compound through the blood–brain barrier (BBB) and subsequent inhibition of γ-aminobutyric acid receptors [22]. In contrast, DARO has limited penetration through the BBB and, thus, a limited effect on mental status. This has been demonstrated in preclinical trials of DARO [23][24]. A study showed that the

penetration rate of ENZA and APA to the BBB was more than 10 times that of DARO [25]. Therefore, DARO has been reported to be safe in patients with a history of seizures [26], and, thus, the ARAMIS trial did not exclude patients with a history of seizures unlike the SPARTAN and PROSPER trials did. In the PROSPER, SPARTAN, and ARAMIS trials, the incidences of seizures in the placebo arms were 0%, 0%, and 0.2%, respectively, whereas those in the intervention (ENZA, APA, and DARO) arms were <1%, 0.2%, and 0.2%, respectively.

Looking at the results of the three studies, all three drugs showed better oncologic outcomes in nm CRPC than placebo did. However, there are no direct comparative studies between the three drugs. Therefore, it is not yet clear which drug is superior among them. Therefore, we tried to indirectly compare the results of the three drugs based on a published network meta-analysis of phase III RCT results [27][28][29][30][31].

2.1. MFS and PSA Progression-Free Survival

In the primary analyses, treatment with APA (HR, 0.28; 95% CI, 0.23–0.35; $p < 0.001$), ENZA (HR, 0.29; 95% CI, 0.24–0.35; $p < 0.001$), or DARO (HR, 0.41; 95% CI, 0.34–0.50; $p < 0.001$) than treatment with placebo as an adjunct to ADT was associated with an approximately two-year increase in median MFS. These results suggest the superiority in oncologic outcomes of the three drugs (APA, ENZA, and DARO) over placebo. According to a published network meta-analysis [28][29][30], the SPARTAN and PROSPER trials showed superiority over the ARAMIS trials in terms of MFS. However, there was no difference in the indirect comparison between APA and ENZA. Although PSA progression-free survival showed similar results, it is difficult to draw conclusions until a direct comparison is made. In a recently published study, DARO was compared with APA and ENZA by selection and reweighting to match the inclusion criteria and baseline characteristics of the patients; however, no statistically significant difference was seen in the MFS [32]. Therefore, a careful interpretation is required.

2.2. OS

In the final analyses, all RCTs showed an improvement in OS with the intervention compared with placebo; the SPARTAN, PROSPER, and ARAMIS trials reported HRs of 0.78 (95% CI; 0.64–0.96; $p = 0.016$), 0.73 (95% CI; 0.61–0.89; $p = 0.001$), and 0.69 (95% CI; 0.53–0.88; $p = 0.003$), respectively. A published network meta-analyses, analyses using the final data of each RCT, were performed by Roumiguie et al. [31]. However, current data are insufficient to assess the significant ranking of the three drugs over placebo in terms of OS. Unlike for MFS and PSA progression-free survival, all three studies showed similar results for OS. Although the ARAMIS trial has not yet reported the median OS, it showed similar OS results compared to a relatively low MFS. However, the OS may eventually differ when the drugs are administered after cancer progression. In the three studies, there were differences in subsequent therapy after nmCRPC progression. As for the choice of the drug used in the subsequent therapy, the SPARTAN trial used abiraterone more frequently than the other two did; the PROSPER trial used abiraterone and chemotherapy at a similar rate, whereas the ARAMIS trial prescribed chemotherapy the most often. The optimal subsequent therapy for CRPC remains controversial [33][34][35][36][37].

2.3. Safety

The SPARTAN trial collected data on AEs at one-month intervals, whereas the PROSPER and ARAMIS trials collected AE-related data at four-month intervals. Compared to the placebo group, the APA group had higher rates of fatigue, HTN, rash, weight loss, arthralgia, and fracture, while the ENZA group had higher rates of fatigue, HTN, dizziness, falls, and fracture. The occurrence of fatigue was higher in the DARO group than in the placebo group.

There was an increase in HTN incidence in the SPARTAN and PROSPER intervention groups. It is a potent inducer of CYP3A4 due to the nature of the drug [38][39], which may be caused by interactions with antihypertensive drugs [40][41]. However, DARO has demonstrated a lower likelihood of drug–drug interactions than those of APA and ENZA because DARO is structurally distinct from the two drugs [24][42]. Cardiotoxicity is an important factor in the use of ENZA [43][44]. A previous meta-analysis showed a significant increase in the relative risk of all-grade and high-grade cardiac toxicity in patients receiving ENZA compared to that in patients receiving placebo [45]. In the PROSPER trial, cardiotoxicity increased by approximately 2% with ENZA than with placebo. APA had no cardiotoxic side effects apart from HTN, and DARO did not differ from placebo in terms of cardiotoxicity.

2.4. Health-Related Quality of Life Outcomes

The ultimate treatment goal for nmCRPC is to maintain the patient's QOL and delay time to metastasis. Therefore, each of the three clinical trials evaluated QOL using a verified questionnaire.

In the SPARTAN trial, health-related QOL (HR-QOL) was assessed using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and European Quality of Life (EQ) visual analog scale (VAS) [46][47]. After 29 months, for FACT-P, the

APA and placebo groups reported mean scores of −0.99 ± 0.98 and −3.29 ± 1.97, respectively. Additionally, for EQ-VAS, the mean scores for the APA and placebo groups were 1.44 ± 0.87 and 0.26 ± 1.75, respectively. There was no statistical difference, but the APA group had slightly better QOL than did the placebo group. In the PROSPER trial, many comparisons were made between placebo and ENZA groups regarding QOL. The FACT-P total score for the ENZA group was significantly better than that for the placebo group (HR 0.83; 95% CI 0.69–0.99; $p = 0.037$). The mean score for the Brief Pain Inventory Short Form, which assesses pain severity, was reported to be better in the ENZA group than in the placebo group (HR 0.75; 95% CI 0.57–0.97; $p = 0.028$). In addition, patients showed better bowel symptoms, function, and urinary symptoms. The HR-QOL with DARO was reported based on preliminary data [48]. DARO significantly delayed pain progression (HR 0.65; 95% CI 0.53–0.79; $p < 0.001$) more than placebo did. Moreover, the delay in urinary symptoms was clinically significant with DARO (HR, 0.64; 95% CI, 0.54–0.76; $p < 0.01$) than with placebo. A recent study compared HR-QOL outcomes between APA and ENZA through matching-adjusted indirect comparisons. They reported that, based on FACT-P scores, APA showed better results than ENZA did [49]. However, since there is no direct comparison between the three drugs yet, it is difficult to evaluate which drug facilitates superior QOL. All three drugs may offer patients with nmCRPC a therapeutic option while maintaining QOL.

3. Conclusions

APA, ENZA, and DARO have excellent safety profiles for patients with nmCRPC. The HR-QOL was preserved and prostate cancer-related symptoms were significantly delayed in the intervention groups. Therefore, APA, ENZA, and DARO should be considered as novel standard therapies for nmCRPC. However, the effects of these three drugs should be compared through direct comparative studies in the future.

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