Clinical and Translational Oncology (2020) 22:1033–1039
https://doi.org/10.1007/s12094-019-02228-2

RESEARCH ARTICLE

Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials

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Received: 28 August 2019 / Accepted: 4 October 2019 / Published online: 15 October 2019

Abstract

Background Novel hormonal therapies have been recently investigated in non-metastatic castration-resistant prostate cancer (CRPC). We performed a meta-analysis to assess the efficacy and safety of novel hormonal therapies in non-metastatic CRPC.

Materials and methods The primary outcome was metastasis-free survival (MFS). The secondary endpoints were overall survival (OS), time to PSA progression and safety. We planned a subgroup analysis according to the PSA doubling time (> 6 vs < 6 months), Eastern Cooperative Oncology Group (ECOG) performance status (1 vs 0) and concomitant use of bone-targeting agent (yes vs no).

Results Pooled analysis of novel hormonal therapies revealed significantly increased MFS compared with placebo (hazard ratio (HR): HR = 0.32, 95% CI 0.25–0.41; $p < 0.00001$). The subgroup analysis showed a statistically significant MFS advantage in favour of men with the lower ECOG performance status. Other secondary endpoints favoured the novel hormonal therapies. The relative risk (RR) of grade ≥ 3 adverse events and ≥ 3 hypertension was 1.31 and 1.39, respectively.

Conclusions This study confirmed the efficacy and safety of the novel hormonal therapies in non-metastatic CRPC.

Keywords Prostate cancer · Enzalutamide · Apalutamide · Darolutamide

Introduction

Prostate cancer is one of the main causes of cancer-related deaths in men [1]. After initial localized and definitive therapy (DT), either with prostatectomy (RP), radiotherapy (RT) or both, it is estimated that between 27 and 53% of all men treated with DT progress to biochemical recurrence at some point in their life [2]. Many of these patients keep on to have an increasing elevation of prostate-specific antigen (PSA) and are managed with androgen-deprivation therapy (ADT) which involves a gonadotropin-releasing hormone (GnRH) agonist or antagonist [3]. Unfortunately, failure of androgen deprivation therapy is nearly unavoidable and a further rising of PSA generally anticipates disease progression [4] although it is not always accompanied by the presence of distal metastases. This pathological entity with the progressive rising of PSA level on continuous ADT (plus a testosterone castrate level) and absence of metastatic lesions on imaging diagnostic tools is called non-metastatic castration-resistant prostate cancer (nmCRPC) [2, 5] and is usually also characterized by increased amplification or expression of the androgen receptor gene [6]. The occurrence of shorter PSA doubling time of CRPC is associated with a shorter time to develop metastasis or death [4, 5] and for those with nmCRPC, the treatment goal is to delay the time to metastasis. The common metastatic site is the bone and is associated with pathologic fracture, pain and spinal cord compression [7, 8]. PSA doubling time and baseline PSA levels are considered the two main risk factors in developing metastasis [9, 10].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12094-019-02228-2) contains supplementary material, which is available to authorized users.

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Until recently, no consensus recommendation was accomplished for the ideal medication of nmCRPC and observation plus first-generation androgen receptor (AR) antagonists, such as flutamide or bicalutamide, or with ketoconazole or estrogens, was the standard of care [11]; nevertheless, none of these therapies was associated with a clear benefit in terms of survival [12–14]. Other early phase 3 clinical trials assessed additional treatment options for nmCRPC but, unfortunately, atrasentan, sodium clodronate and zoledronic acid did not show a survival benefit in patients with nmCRPC [15–17]. Denosumab, although its reported efficacy and MFS benefit, it did not show an improvement concerning the overall survival (OS) and finally, it was not provided with FDA approval because of its toxic properties and not significant improvement in MFS [10, 18].

However, this scenario is destined to change thanks to the introduction of novel hormonal therapy based on non-steroidal drugs that possess the ability to retain antagonism in cells overexpressing androgen receptors and have shown a significantly longer metastasis-free survival (MFS) time compared with placebo [19–21]**.** In fact, either enzalutamide or apalutamide, second-generation androgen receptor antagonists, have demonstrated to prolong MFS compared with placebo for men with nonmetastatic CRPC [19, 20]**.** Finally, darolutamide, an androgen-receptor antagonist, with a different structure from enzalutamide and apalutamide, was confirmed as an active agent in non-metastatic CRPC [21]. These novel drugs are changing the treatment landscape for nmCRPC patients [17].

In this meta-analysis, the efficacy and safety from randomized controlled trials (RCTs) of novel hormonal therapy in patients with non-metastatic CRPC have been in-depth analyzed and reported. Finally, possible clinical predictors of efficacy have been investigated and future direction treatments are discussed.

Materials and methods

Data retrieval strategies

We conducted a literature-based meta-analysis of RCTs in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines [22]**.** Relevant publications from PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) Meeting were identified using the following search terms: "prostate cancer", "castration-resistant prostate cancer", "non metastatic", "enzalutamide", "apalutamide", and "darolutamide" (Supplementary files). Publications available in these databases up to March 1, 2019, were analyzed. The search criteria were limited to articles of phase III or phase II RTCs. The computer search was supplemented with a manual search of the primary studies referenced in all of the retrieved review articles. When the results of a study were reported in subsequent analysis, only the most recent and complete version was included in this meta-analysis. The protocol for this systematic review was registered on the PROSPERO International prospective register of systematic reviews (CRD42019129545) and is available in full on the website at https://www.crd.york.ac.uk/PROSPERO.

Inclusion criteria

Two authors screened the studies according to inclusion/exclusion criteria, the contentious studies were made in consultation with the corresponding author. The studies were identified according to the following inclusion criteria: (1) participants with non-metastatic CRPC; (2) a novel hormonal therapy as the experimental drug; (3) the presence of a control arm for comparison; (4) a primary outcome of MFS expressed as the hazard ratio (HR) and secondary outcomes of overall survival (OS) expressed as the HR, time to PSA progression expressed as the HR and safety expressed as relative risk (RR). The following exclusion criteria were used: (1) insufficient data available to estimate the outcomes; (2) animal studies; (3) the size of each arm < 10 participants; (4) non-randomized studies. Two authors independently extracted the relevant data from the studies.

Quality assessment and statistical analysis

Study quality was assessed using the Jadad 5-item scale, taking into account randomisation, double-blinding and withdrawals. The final score ranged from 0 to 5 [23]. In the event of disagreements, the consensus was achieved in discussion with the corresponding author (GR).

Statistical analysis

The statistical analyses were performed with Revman 5.3. The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird method) [24, 25] depending on the absence or presence of heterogeneity. Statistical heterogeneity was assessed with the Q test and the I^2 statistic. I^2 values of 25%, 50% and 75% were considered to indicate low, moderate and high heterogeneity, respectively [26]. When $P > 0.1$ and $I^2 < 50\%$, the fixed-effects model was used; otherwise, the random-effects model was used. For the time-to-event variables, HRs with 95% confidence intervals (CI) were calculated for each study. For the dichotomous variables, RRs with 95% CIs were calculated for each study. A subgroup analysis was performed to highlight any differences between studies according to PSA doubling time (> 6 vs < 6 months), ECOG (1 vs 0) and concomitant use

of bone-targeting agent (yes vs no). For all the statistical analyses, a value of $P < 0.05$ was regarded as statistically significant, and all tests were two-sided.

Results

Literature review and characteristics of the included studies

The search yielded 2345 potentially relevant articles. Nine hundred and sixty-nine studies were excluded as duplicates. After viewing the titles and abstracts of the 1376 remaining studies, the full text of 15 studies was retrieved and 3 studies [19–21] were ultimately included in the analysis (Figure 1S). A total of 4117 cases were included; among these, 2694 cases were in the experimental group and 1423 cases in the control group**.** All the studies were randomized, double-blind, placebo-controlled, phase 3 trials. The characteristics of the studies included in the meta-analysis and the definition of secondary outcomes are summarized in Table 1. Median Jadad score was five, confirming a high level of quality (Table 1). Due to the small number of trials that were included, no publication bias was estimated.

Primary endpoint

After a mean follow-up of 18 months across all included studies (Table 2). The pooled analysis revealed that these novel hormonal therapies showed a significantly improved MFS (HR = 0.32, 95% CI 0.25–0.41; $P < 0.00001$, I^2: 79%; Fig. 1). The subsequent subgroup analysis according to PSA doubling time (>A total of 4117 cases were 6 vs <6 months) revealed that MFS was significantly improved with a similar extent (HR = 0.34 vs HR = 0.32; Figure 2S). The pooled analysis according to ECOG performance status (1 vs 0) revealed that MFS was significantly improved with a greater extent in men with ECOG: 0 (HR = 0.30 vs HR = 0.45; Figure 3S). Finally, the pooled analysis according to the concomitant use of bone-targeted agents (yes vs no) revealed that MFS was significantly improved with a similar extent (HR = 0.36 vs HR = 0.33; Figure 4S).

Secondary endpoints

Data on secondary endpoints are reported in Table 2. The pooled analysis revealed that new novel hormonal therapies significantly improved OS (HR = 0.74, 95% CI 0.61–0.91; $P = 0.004$) (Fig. 2) compared with placebo. The fixed-effect model was used for the absence of heterogeneity ($I^2 = 0\%$) for this endpoint between the trials. Time to PSA progression (HR = 0.08, 95% CI 0.05–0.14; $P < 0.00001$; $I^2 = 95\%$) was also significantly improved with a novel hormonal agent

Table 1 Characteristics of the included studies

Trials	Treatment arms	Cases	Endpoints	Setting	Jadad Score
ARAMIS	Darolutamide vs placebo	955	Primary: metastasis free survivor	Non metastatic castration-resistant prostate cancer (PSA doubling time of 10 months or less)	5
		554	Secondary: overall survival, time to pain progression, time to cytotoxic chemotherapy, time to a symptomatic skeletal event		
PROSPER	Enzalutamide vs placebo	933	Primary: metastasis free survivor	Non metastatic castration-resistant prostate cancer (PSA doubling time of 10 months or less)	5
		468	Secondary: time to PSA progression, PSA response-rate, time to the first use of a subsequent antineoplastic therapy, quality of life, overall survival, safety		
SPARTAN	Apalutamide vs placebo	806	Primary: metastasis free survivor	Non metastatic castration-resistant prostate cancer (PSA doubling time of 10 months or less)	5
		401	Secondary: time to metastasis, progression free survival, overall survival, time to symptomatic progression, time to the initiation of cytotoxic chemotherapy		

Table 2 Data on metastasis-free survival, median treatment duration and a median follow-up of the included studies

Study	Median MFS (months)	Median treatment duration (months)	Median follow-up (months)
ARAMIS	40.4 vs 18.4	14.8 (D)	17.9
D vs PL	HR: 0.41	11 (PL)	
PROSPER	36.6 vs 14.7	18.4 (E)	18.5 (E)
E vs PL	HR: 0.29	11.1 (PL)	15.1 (PL)
SPARTAN	40.5 vs 16.2	NR	20.3
APA vs PL	HR: 0.28		

MFS metastasis-free survival, *OS* overall survival, *HR* hazard ratio, *NR* not reported, *E* enzalutamide, *PL* placebo, *BIC* bicalutamide, *D* darolutamide, *APA* apalutamide

the RR of a grade ≥ 3 adverse effects was higher with novel hormonal therapies compared to placebo (RR = 1.31, 95% CI 1.18–1.45; $P < 0.001$). Other toxicities are reported in Table 4. Of note, we found a statistically significant increase of RR for hypertension any and ≥ 3 grade and fatigue any grade.

Discussion

Although the treatment scenario of metastatic CRPC has been recently revolutionized by the approval of several agents able to increase survival [27–29], none of these agents is curative and the median survival is around 36 months [30]. Therefore, in the specific setting of non-met-

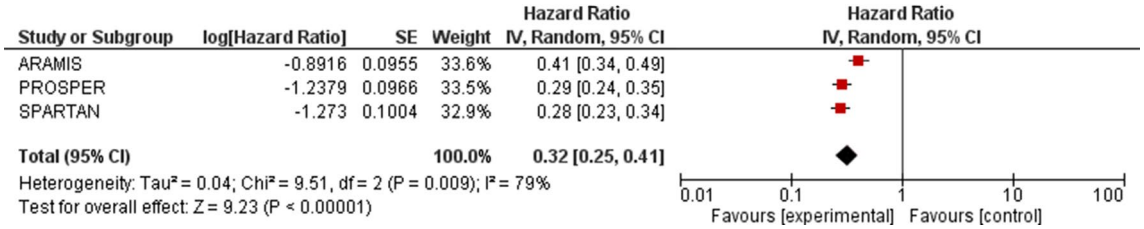

Fig. 1 Forest plots of hazard ratios (HRs) for metastasis-free survival (MFS) comparing novel hormonal therapy to placebo

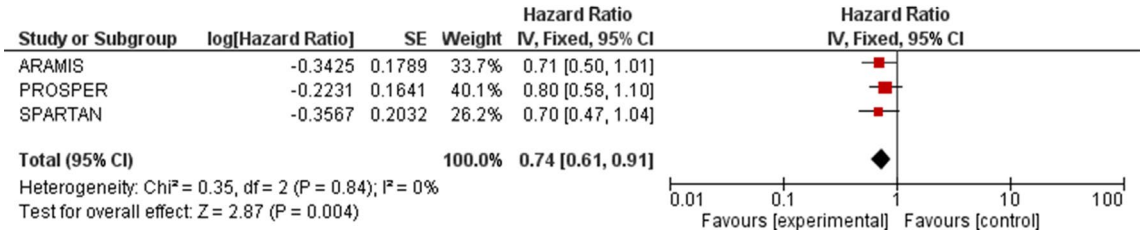

Fig. 2 Forest plots of hazard ratios (HRs) for overall survival (OS) comparing novel hormonal therapy to placebo

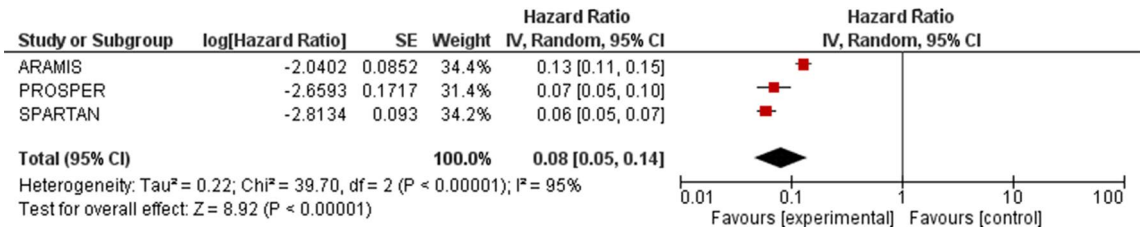

Fig. 3 Forest plots of hazard ratios (HRs) for time to PSA progression comparing novel hormonal therapy to placebo

(Fig. 3). The incidence of severe adverse events (grade 3–4) ranged from 25 to 45% in the experimental group and 19 to 34% in the control group, respectively (Table 3). The pooled analysis with a random-effects model revealed that

astatic CRPC, the use of novel hormonal agents to delay the time to metastasis may prolong survival and cancer-related complications [31]. To the best of our knowledge,

Table 3 Secondary outcomes of the included studies

Study	Median OS (months)	Median time to PSA progression (months)	Adverse event leading to death (%)	Any adverse event ≥ 3 (%)
ARAMIS	Not reached	33.2 vs 7.3	3.9 vs 3.2	24.7 vs 19.5
D vs PL	HR 0.71	HR 0.13		
PROSPER	Not reached	37.2 vs 3.9	3 vs 1	31 vs 23
E vs PL	HR 0.80	HR 0.07		
SPARTAN	Not reached vs 39	Nor reached vs 3.7	1.2 vs 0.3	45.1 vs 34.2
APA vs PL	HR 0.70	HR 0.06		

MFS metastasis-free survival, *OS* overall survival, *HR* hazard ratio, *NR* not reported, *E* enzalutamide, *A* abiraterone, *P* prednisone, *PL* placebo, *BIC* bicalutamide

Table 4 Adverse events

	HR	95% CI	*P* value	I^2 (%)	*P* value	Model
Any adverse event Grade 1–4	**1.08**	1.02–1.14	0.01	79	0.008	Random
Any adverse event Grade ≥ 3	**1.31**	1.18–1.45	< 0.001	0	0.93	Fixed
Serious adverse event Grade 1–4	**1.21**	1.07–1.37	0.002	0	0.38	Fixed
Adverse event leading to discontinuation of the trial regimen	**1.30**	1.05–1.62	0.02	35	0.22	Fixed
Adverse event leading to death	2.67	0.79–9.02	0.11	70	0.04	Random
Fatigue Grade 1–4	**1.69**	1.19–2.39	0.003	82	0.004	Random
Fatigue Grade ≥ 3	1.85	0.38–9.14	0.45	71	0.03	Random
Hypertension Grade 1–4	**1.50**	1.03–2.18	0.03	70	0.04	Random
Hypertension Grade ≥ 3	**1.39**	1.07–1.81	0.01	13	0.32	Fixed

Statistically significant values are in bold

HR hazard ratio, *CI* confidence interval

the present study is the first literature-based meta-analysis of 3 RCTs with more than 4000 patients that summarizes the efficacy and safety of novel hormonal therapies for the treatment of non-metastatic CRPC. Our results revealed a reduction in the risk of time to development of metastasis in almost 70% of patients and a reduction in death and time to PSA progression in 26% and more than 90% of patients respectively. Of note, we showed that novel hormonal agents prolong OS in a statistically significant fashion, and although median OS (still not reached in all experimental arms) and the short follow-up preclude from definitive conclusions, we confirm the use of novel hormonal agents to prolong survival of non-metastatic CRPC. The absence of heterogeneity further supports this data.

Interestingly, the planned subgroup analysis according to PSA doubling time (> 6 vs < 6 months), ECOG (1 vs 0) and concomitant use of bone-targeting agent (yes vs no) showed no consistent difference in terms of MFS regardless of the PSA doubling time and the use of concomitant bone-targeting agents. Conversely, when patients with ECOG performance status of 0 have been compared to patients with ECOG performance status of 1 a statistically significant MFS advantage has been found with novel hormonal agents in favour of men with the lower ECOG performance status (HR: 0.30 vs 0.45 respectively, Figure 3S). The absence of heterogeneity for ECOG:0 subgroup further supports these data. Therefore, further investigations for the subgroup of patients with ECOG > 0 are awaited to define the optimal role of novel hormonal agents in non-metastatic CRPC.

According to toxicity, the pooled analysis with a fixed-effects model revealed that the incidence of a grade ≥ 3 adverse event was moderately higher with novel hormonal therapies (RR = 1.31). In addition, although an increase in adverse events associated with death has been observed, this result did not reach statistical significance. Therefore, our data confirm the safety profile of novel hormonal therapies [27, 30–32]. However, in line with previous studies [33], we

reported an increase in the RR of hypertension > 3. Interestingly, our meta-analysis is in line with another recent paper by Di Nunno et al. [34].

The present meta-analysis has several limitations. There were only three studies, and these studies exhibited very high levels of heterogeneity for some of the endpoints. It should be noted that no active comparator was used in all the evaluated trials. Furthermore, only two secondary endpoints were not evaluated in our meta-analysis and the adverse event analysis was limited to fatigue and Hypertension with different versions of Common Terminology Criteria for Adverse Events (CTCAE) used across the three studies. Finally, our meta-analysis was based on the literature rather than on individual patients' data, however, it was a large sample size with more than 4117 patients in total (2694 in the experimental arm).

Conclusions

Currently, the use of novel hormonal agents has been widely validated for metastatic CRPC in the chemotherapy-naïve and post-chemotherapy settings. Our literature-based meta-analysis supports the existing evidence to target the androgenic pathway for also non-metastatic CRPC, further studies are awaited to discover predictive markers of efficacy and the best candidate for this approach.

Funding No funding.

Compliance with ethical standards

Conflict of interest The other authors declare that there are no conflicts of interest in this work.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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