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MINI-REVIEW

Improving quality of life in metastatic castration-resistant prostate cancer: the role of androgen receptor axis-targeted agents

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Abstract

Androgen receptor axis-targeted agents (ARTAs), specifically enzalutamide and abiraterone acetate, have significantly extended the survival of men with metastatic castration-resistant prostate cancer (mCRPC), making them the standard of care for mCRPC. In addition, the impact of both drugs on the health-related quality of life (HRQoL) represents an important therapeutic objective of mCRPC patients. This article aimed to review clinical evidence of HRQoL in mCRPC men treated with abiraterone acetate and enzalutamide and identify their potential benefits and correlation with overall survival or disease progression based on a literature search of randomized clinical trials, studies from real clinical practice and professional guidelines up to October 2022. The synthesized evidence showed that HRQoL of both novel hormonal therapies (NHTs) was evaluated as a secondary endpoint in pivotal trials. The results revealed that these novel agents might improve the HRQoL of mCRPC patients. However, it was difficult to compare the results between trials due to inconsistencies in trial designs and instruments. Correlation tests showed a positive correlation with HRQoL and clinical efficacy outcomes. Patient perspective was assessed only in a few comparative trials. In conclusion, both abiraterone acetate and enzalutamide improved the HRQoL of mCRPC patients. Nevertheless, further research is warranted as there was a limited number of head-to-head trials directly comparing the overall effects of ARTAs for mCRPC.

Keywords

Quality of life; Abiraterone; Enzalutamide; Castration-resistant prostate cancer

1. Introduction

Novel hormone therapies (NHTs) targeting the androgen receptor (AR), known as androgen receptor axis-targeted agents (ARTAs), such as enzalutamide and abiraterone acetate, have demonstrated significant efficacy in both prolonging the overall survival (OS) and delaying disease progression of metastatic castration-resistant prostate cancer (mCRPC), making them the current standard of care for treating mCRPC patients [1–4]. Evaluating the effects of various therapeutic options on health-related quality of life (HRQoL) has become an important therapeutic endpoint in clinical trials, including registration studies for both ARTAs. HRQoL represents a multicomponent concept encompassing several aspects of a patient's life. However, defining the quality of life and comprehensively assessing or quantifying the several domains affecting patients' survival remain challenging. Thus, there is no established standard for assessing HRQoL in cancer patients, specifically for prostate cancer patients. Encouragingly, several tools have been developed to assess the functional, physical, social and emotional domains of these patients. Moul *et al*. [5] conducted a literature review on this topic and provided an overview of the most frequently used HRQoL questionnaires in the field of prostate cancer. Of the 17 clinical trials assessed, 8 different quality of life questionnaires were identified: the Functional Assessment of Cancer Therapy-Prostate (FACT-P), the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30-Prostate Cancer Module (EORTC QLQ-C30-PR25), Prostate Cancer-Specific Quality of Life Instrument (PROSQOLI), Quality of Life Module-Prostate 14 (QOLM-P14), European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTCQLQ-C30), Functional Assessment of Cancer Therapy-General (FACT-G), Functional Living Index-Cancer (FLIC), and the European Quality of Life-5 Dimensions (EQ-5D) [5]. The EORTC QLQ-C30 is a 30-item, cancer generic instrument designed to assess the functional status, global health status, symptoms and financial difficulties associated with the disease. The EORTC QLQ-C30 comprises a prostate cancer module, the QLQ-PR25, which consists of 25 items focusing on urinary symptoms, bowel symptoms, sexual functioning, and treatment-related adverse events. QOLM-P14 is a self-

assessing instrument developed for use with the QLQ-C30 to evaluate prostate-specific characteristics such as pain impact on mobility, pain relief, drowsiness, hair loss, change in taste, urinary symptoms, and sleep disturbance [5]. FACT-P is a 39-item questionnaire consisting of both a general assessment of HRQoL called FACT-G with 4 multi-item subscales (physical, social/family, emotional, and functional well-being) and Prostate Cancer Subscale (PCS) with 12 items (assess prostate-related problems that include sexuality, bowel/bladder function, and pain) [5–9]. PROSQOLI is a prostate-specific questionnaire evaluating 10 items, including symptoms, functioning and overall well-being, measured at linear analog self-assessment scales. EQ-5D represents a generic questionnaire that assesses the 5 dimensions of health. FLIC is a generic cancer instrument evaluating 22 items based on physical and psychological well-being, symptoms and the disease's impact on patients' families [5]. FACT-P is a standardized tool that has been validated for use in the mCRPC population [6–9]. The questionnaire has been used in all registration studies evaluating both abiraterone acetate and enzalutamide in mCRPC. However, even with the same tool, different assessment schedules may be applied, making indirect comparisons of study results challenging. In addition, the number of clinical trials comparing the two ARTA drugs to determine which treatment is more beneficial in terms of quality of life remains limited.

2. Methods

We performed a literature search of studies evaluating or comparing the HRQoL of mCRPC patients treated with abiraterone acetate or enzalutamide. The PubMed database was searched for publications and clinical practice guidelines using pre-defined keywords, including health-related quality of life, prostate cancer, abiraterone acetate and enzalutamide. We screened the title and abstract of each retrieved article and selected only those that evaluated the impact of abiraterone acetate and/or enzalutamide on the HRQoL of mCRPC patients. Collectively, of the 22 publications included in this study, 16 assessed HRQoL in mCRPC patients, including 5 pivotal randomized clinical trials with abiraterone acetate or enzalutamide in mCRPC, and 11 associated publications with analyses of secondary or exploratory endpoints on quality of life (n = 7 for abiraterone acetate and n = 4 for enzalutamide). Six of the 22 publications directly compared the treatment effects of abiraterone acetate and enzalutamide, including HRQoL analysis. Other ARTAs, such as darolutamide and apalutamide, were not included in the review as neither drug is registered for mCRPC settings.

3. HRQoL assessment in pivotal trials

3.1 Quality of life assessment-abiraterone acetate

Patients' quality of life in a registration study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy (COU-AA-301), was assessed using the FACT-P instrument. Individual analyses were prespecified. Patient cooperation in completing the questionnaires was high (91.3% at cycle 28). Baseline FACT-P scores were comparable in both groups. Quality of life analysis using the FACT-P questionnaire showed that treatment with abiraterone acetate in combination with prednisone led to a clinically significant improvement in HRQoL domains compared to prednisone alone, except for the social/family well-being subscale. Abiraterone acetate therapy also led to a significantly shorter median time to HRQoL improvement in the physical well-being domain and the so-called Trial Outcome Index (TOI). In terms of time to deterioration in FACT-P scores, treatment with abiraterone acetate significantly delayed the deterioration in quality of life compared to the control group (59.9 weeks versus 36.1 weeks; $p < 0.0001$), both in the total FACT-P score and in all FACT-P subscales except the social/family well-being domain. The FACT-P total score was improved in 48% of patients receiving abiraterone acetate compared to 32% in those with prednisone alone ($p < 0.0001$). Repeated measures analysis demonstrated that changes in total FACT-P score from baseline were significantly better in the abiraterone acetate arm compared to the prednisone arm ($p < 0.05$ in cycles 2–7, 10, 13–17, 19, 22, 23, and 26) [10].

The COU-AA-301 trial is the first study on mCRPC to assess fatigue using a validated fatigue assessment tool [11]. The Brief Fatigue Inventory (BFI) was used to assess fatigue intensity and interference. The results showed that patients with clinically significant fatigue at baseline and treated with abiraterone acetate in combination with prednisone had statistically significant improvement in fatigue intensity and interference compared to those in the control arm. The percentage of patients with improvement in fatigue intensity was 58.1% versus 40.3% ($p = 0.0001$), and that for improvement in fatigue interference was 55% versus 38% ($p = 0.0075$) for the abiraterone acetate versus the control arm, respectively. The time to improve fatigue intensity was also shorter in the abiraterone acetate arm compared to placebo, with a median of 59 days versus 194 days ($p = 0.0155$) [11].

Pain relief was achieved in a higher proportion of patients in the abiraterone acetate arm than in the control arm: 45% *vs.* 28.8% ($p = 0.0005$). Patients in the abiraterone acetate group experienced faster pain intensity relief than the control group (median time to pain palliation, 5.6 months *vs.* 13.7 months; $p = 0.0018$) [12].

The COU-AA-302 study assessed the effect of abiraterone acetate treatment on the HRQoL of chemo-naive mCRPC patients using the FACT-P instrument. The baseline pain and functional status scores were similar in both arms. Patient compliance with the completion of the pain questionnaire (Brief Pain Inventory-Short Form: BPI-SF) and HRQoL questionnaire (FACT-P) was high (>95% for both assessment tools). Patients in the abiraterone acetate arm demonstrated a statistically significant improvement in pain interference compared to patients treated with prednisone alone ($p = 0.005$) [13]. However, no statistically significant difference was observed in the delay of progression in average and worst pain intensity between the abiraterone acetate and prednisone groups ($p = 0.061$ and $p = 0.1$, respectively) [14].

Further analysis showed that abiraterone acetate delayed

the degradation of the FACT-P total score compared to the control group (median time to delayed FACT-P degradation, 12.7 months *vs.* 8.3 months; $p = 0.005$). A statistically significant result was also observed in the prostate cancer-specific scale (PCS), which demonstrated a significantly longer median time to PCS worsening in the abiraterone acetate arm compared to the control arm (11.1 months *vs.* 5.8 months; $p < 0.0001$). A statistically significant delay in worsening of HRQoL in favor of abiraterone acetate compared to the control group was also observed for the other domains of the FACT-P questionnaire, including physical well-being score, functional well-being score and emotional well-being score ($p = 0.002$). However, the difference in regard to social/family well-being score was not significant ($p = 0.6$) (13). The HRQoL outcomes of the patients in the COU-AA-302 study were also assessed longitudinally using the repeated measures method (mixed-effects model for repeated measures). With repeated measurement, significant changes were observed during the first year of treatment in favor of abiraterone acetate in the FACT-P total score, TOI and PCS scores, as well as in the functional, physical and emotional domains, thereby confirming the sustained improvement in HRQoL with abiraterone acetate therapy [15].

3.2 Analysis of the relationship between HRQoL and OS from studies with abiraterone acetate

In 2016, the results of the relationship between patient reported outcomes (PROs) and clinical efficacy endpoints from both registration studies of abiraterone acetate, COU-AA-301 and COU-AA-302, were published, using data from a total of 2283 patients (1195 and 1088 patients in the respective studies). Regression models were constructed to determine the association between fatigue, pain, physical and functional well-being, prostate cancer subscale (PCS), OS and radiographic progression-free survival (rPFS) over the first 181 days in the studies, regardless of treatment. Since patients in the COU-AA-301 trial were more symptomatic and had more advanced-stage disease, the improvement in PROs was assessed. Patients (chemo-naive) in the COU-AA-302 trial were asymptomatic or mildly symptomatic, and for the purpose of analysis, the worsening of PROs was also assessed. The COU-AA-301 trial showed that men with improved PROs experienced a significant reduction in the risk of death and rPFS ($p < 0.0001$) compared to patients who experienced worsening or stable PROs scores. In the COU-AA-302 trial, patients with worsening PROs were found to have a significantly higher risk of disease progression ($p < 0.02$) compared to patients with improved or stable PROs scores. The impact of PROs on OS was not assessed due to insufficient events at the time of analysis [16].

3.3 Quality of life assessment-enzalutamide

The secondary endpoints of a registration study of enzalutamide in patients with prostate cancer who had previously been treated with one or two chemotherapy regimens, at least one of which contained docetaxel (AFFIRM study) also evaluated the FACT-P response (improvement of the FACT-P total score by ≥ 10 points compared to the baseline score). The results showed that the FACT-P response and median time to deterioration of HRQoL in patients treated with enzalutamide were significantly superior to those with placebo (42% *vs.* 15% ($p < 0.0001$), and 9.0 months *vs.* 3.7 months (Hazard Ratio (HR) 0.45; 95% Confidence Interval (CI): 0.37–0.55, $p < 0.0001$)). The AFFIRM study also included analysis of the effect of treatment on pain. Pain progression at week 13 was observed in 28% patients taking enzalutamide in comparison to 39% patients in the control arm (difference assessed by Pain Diary, −11.2%; $p = 0.0018$). The median time to pain progression was not reached in men treated with enzalutamide and was 13.8 months in the control group, representing a demonstrated benefit of enzalutamide (HR 0.56; $p = 0.0004$) [17]. Pain palliation at week 13 was achieved in 22 (45%) of the 49 evaluable patients taking enzalutamide compared with 1 (7%) of 15 patients taking placebo (difference assessed by Pain Diary, 38.2%; $p = 0.0079$). Quality of life analysis in the AFFIRM trial demonstrated that treatment with enzalutamide led to pain palliation in a higher proportion of patients compared to placebo (45% *vs.* 7%). Enzalutamide reduced the relative risk of pain progression by 44% compared to placebo ($p = 0.0004$) and had a beneficial effect on all FACT-P domains [17].

Loriot *et al.* [18] assessed the HRQoL of patients in the PREVAIL (enzalutamide in chemotherapy-naive mCRPC patients) study using the FACT-P and EQ-5D (European Quality of Life-5 Dimensions) questionnaires at baseline and during treatment. Baseline HRQoL scores of the enrolled patients measured by FACT-P were comparable in both treatment arms, and patient cooperation in completing the questionnaires was high in both groups for all questionnaires (>90%). Mixed-effect analysis showed significant differences in HRQoL scores assessed by the FACT-P instrument for most domains and on the EQ-5D visual analog scale (VAS) in favor of enzalutamide-treated patients compared to the control arm. In the enzalutamide arm, there was no clinically significant reduction in HRQoL (based on established minimal clinically important differences MID: −6 to −10) on the FACT-P total score and PCS score. However, there was a decrease below the lower limit of clinically meaningful worsening in HRQoL for both of the above scores in the control group. The median time to FACT-P deterioration was 11.3 months in the enzalutamide arm and 5.6 months in the placebo arm, representing a statistically significant benefit and a 38% reduction in risk of HRQoL deterioration in favor of enzalutamide (HR 0.62; $p < 0.0001$). Median time to deterioration in PCS score was longer in the enzalutamide arm than in the control arm (5.7 months *vs.* 2.8 months; $p < 0.0001$). Enzalutamide delayed the time to first deterioration compared to placebo in all other FACT-P subscale scores [18]. Significantly more enzalutamide-treated patients reported clinically meaningful improvements in FACT-P total score, health status index (EQ-5D utility index), and EQ-5D VAS score compared to the control group: 40% *vs.* 23% (FACT-P total score), 28% *vs.* 16% (health status index), 27% *vs.* 18% (VAS), significance level $p < 0.001$ was reached for all parameters assessed). When compared to placebo, treatment with enzalutamide resulted in delayed deterioration of the health status index (EQ-5D utility index), with a median of 19.2 months for enzalutamide *vs.* 11.1 months for placebo

(HR: 0.62; $p < 0.0001$). The EQ-5D VAS results also showed that enzalutamide could significantly delay the progression of the condition by 22.1 months compared to 13.8 months in the control arm ($p < 0.0001$) [18]. The median time to progression of worst pain was 5.7 months in the enzalutamide arm and 5.6 months in the control arm (HR 0.62; $p < 0.0001$). Progression of worst pain at week 13 was fewer in patients taking enzalutamide than those taking placebo (29% *vs.* 42%; $p < 0.0001$). Changes at week 25 were non-significant between the two groups [18].

The quality of life of patients treated with enzalutamide compared to bicalutamide (active arm) was evaluated in the TERRAIN trial (chemotherapy-naive mCRPC patients) using the FACT-P tool and the EQ-5D, the same instruments as in the PREVAIL study. The results, in terms of the FACT-P total score and its individual domains, showed that a greater number of patients treated with enzalutamide experienced an improvement in HRQoL as compared with bicalutamide [19]. At week 61, there was a smaller decrease in HRQoL scores in enzalutamide-treated patients compared with bicalutamide. Clinically meaningful worsening was observed only in the bicalutamide arm. The median time to first quality-of-life deterioration was longer in the enzalutamide arm than in the bicalutamide arm in all subscales except the physical well-being domain. The reduction in risk of deterioration of the FACT-P total score was 36% in favor of enzalutamide (HR: 0.64; $p = 0.007$), with a median time to FACT-P total score deterioration of 13.8 months in the enzalutamide arm versus 8.5 months in bicalutamide arm. Enzalutamide also delayed the deterioration of the health index score (EQ-5D utility index) compared to bicalutamide (14.3 months *vs.* 10.9 months; $p = 0.02$) [20].

3.4 Analysis of the relationship between HRQoL and OS from the AFFIRM Study

Miller *et al*. [21] conducted an analysis to evaluate the association of HRQoL with the disease progression (rPFS) and overall survival (OS) based on data from the AFFIRM study. The univariate analysis showed that higher baseline FACT-P total score and individual domain scores were associated with reduced risk of death (HR 0.78–0.84; $p < 0.01$) and rPFS (HR 0.90–0.94; $p < 0.01$). Further, multivariate analysis showed that the total FACT-P score at baseline and the functional well-being score were predictive factors for OS, while only the total FACT-P score was a predictive factor for rPFS. Each 10-point increase in the total FACT-P score was associated with a 19% reduction in the risk of death (HR 0.81; 95% CI: 0.78–0.84). Each 3-point increase in the physical, functional domain and PCS was associated with 8%, 14% and 9% reductions in the risk of death, respectively [21].

4. HRQoL assessment in comparative trials

A direct comparison of quality of life or patient-reported outcomes (PROs) in chemotherapy-naïve mCRPC patients treated with abiraterone acetate combined with prednisone or enzalutamide was the focus of the prospective, observational, multicenter, non-randomized, 2-arm, phase 4 AQUARIUS study.

The study aimed to assess the impact of abiraterone acetate and enzalutamide treatment on patients' functioning and investigate the potential differences in HRQoL, pain, fatigue and cognitive function in patients treated with ARTA drugs in real-world clinical practice over 12 months using the EORTC QLQ-C30 questionnaire (to assess quality of life), the FACT-Cog questionnaire (to assess cognitive function), the BFI-SF instrument (to assess fatigue), and the BPI-SF questionnaire (to assess pain). The questionnaires were analyzed for the following time periods: 1, 2, 3, 4–6, 7–9 and 10–12 months [22]. The study's primary objectives were the mean change in PROs from baseline, the percentage of patients who experienced at least one clinically meaningful worsening (CMW) compared with improvement or no change in PROs scores. The time to first clinically meaningful worsening in PROs and treatment safety were also assessed [23]. The total number of patients enrolled was 211, comprising 105 in the abiraterone acetate group and 106 in the enzalutamide group. In both treatment arms, all baseline PROs were comparable with no significant difference except for pain interference, although the difference was not clinically significant. Patient cooperation with completing the questionnaires at month 12 was very good (>80%) [23]. After treatment initiation, 18 PROs were significantly more favorable in the abiraterone acetate group than the enzalutamide group ($p < 0.05$). Using a more conservative approach (*i.e.*, statistically significant difference recorded in at least three consecutive periods), 9 of the 18 PROs were found to significantly favor abiraterone acetate compared to enzalutamide. These items comprised cognition, fatigue, loss of appetite, and nausea. Consistency was observed between the different assessing tools for items related to cognitive function and fatigue. A statistically significant difference in favor of abiraterone acetate was confirmed for the following items: perceived cognitive impairment, cognitive impairment based on observation by others (FACT-cog questionnaire) and cognitive functions (QLQ-C30 questionnaire), which were observed in period 1. In addition, similar differences were observed for the fatigue-related items, which included worst fatigue, usual level of fatigue, current fatigue, and fatigue (QLQ-C30) [23]. Statistically significant changes identified in the analysis of changes in PROs values from baseline (as described above) were further examined for clinical significance using the clinically meaningful worsening (CMW) analysis over 12 months. Overall, a significantly lower proportion of patients in the abiraterone acetate group compared to the enzalutamide group experienced at least one episode of CMW in regard to perceived cognitive impairment (49% *vs.* 79%; $p = 0.005$), cognitive impairment based on observation by others (32% *vs.* 62%; $p < 0.001$), worst fatigue (53% *vs.* 79%; $p = 0.008$), fatigue (45% *vs.* 74%; $p = 0.001$) and loss of appetite (36% *vs.* 60%; $p = 0.023$). These differences were observed within 1 month of treatment. Significant differences in CMW favoring abiraterone acetate were also observed in emotional, functional and physical functioning and current pain. The incidence of fatigue and asthenia was lower in patients taking abiraterone acetate compared to those taking enzalutamide (5% *vs.* 15% and 10% *vs.* 11%, respectively) [23].

In 2018, Khalaf *et al*. [24] published the results of a randomized phase 2 trial comparing the therapeutic effects of

abiraterone acetate versus enzalutamide in men with mCRPC. Both ARTA drugs demonstrated comparable efficacy based on the time to disease progression. The secondary objectives of this study were to assess HRQoL, depressive symptoms, and cognitive function. A total of 202 patients were enrolled, and the study assessment was based on FACT-P, the Patient Health Questionnaire-9 (PHQ-9) and the Montreal Cognitive Assessment (MoCA). The results in each domain of the FACT-P questionnaire were evaluated for the age groups <75 and ≥75 years. The results showed that baseline characteristics were balanced except for age (the median age of men in the abiraterone acetate arm was 72.9 years *vs.* 77.6 years in the enzalutamide arm) and that the baseline FACT-P scores were comparable in both treatment groups. Changes in FACT-P scores over time from baseline were more favorable in the abiraterone acetate arm versus the enzalutamide arm in patients ≥75 years of age ($p = 0.003$). No significant difference was observed in younger patients. Clinically meaningful worsening in HRQoL was observed for most domains, and their representation was more or less similar in some patients. However, a significantly higher proportion of patients in the enzalutamide arm experienced clinically meaningful worsening in the physical and functional domains compared to the abiraterone acetate arm (37% *vs.* 21%, $p = 0.013$; 39% *vs.* 23%, $p = 0.015$) [24].

Parimi *et al*. [25] conducted a randomized phase 2 study to examine the effects of abiraterone acetate versus enzalutamide and their sequences in men with mCRPC. The authors focused on evaluating the worsening of depressive symptoms and cognitive function using the PHQ-9 and MoCA questionnaires in 60 patients, among whom 27 were randomized to the abiraterone acetate group and 30 to the enzalutamide group. The study revealed that the worsening of depression scores over the course of the treatment was observed in significantly more patients taking enzalutamide compared to those treated with abiraterone acetate ($p = 0.03$). A trend in cognitive impairment increase was observed in the enzalutamide group compared to the abiraterone acetate group [25].

Fatigue, quality of life and metabolic changes in men treated with first-line

enzalutamide versus abiraterone plus prednisolone for metastatic castration resistant prostate cancer were evaluated in a randomized, single-center, open-label phase 4 study conducted in Denmark (HEAT study). The HEAT trial compared the difference in fatigue change (primary endpoint; assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire) and HRQoL (assessed using the FACT-P tool), body composition, weight, glucose levels, lipids and blood pressure in mCRPC patients treated with enzalutamide versus abiraterone acetate combined with prednisone. The outcomes were measured at baseline and at the 12-week follow-up. The study comprised 170 patients assigned in a 1:1 ratio to enzalutamide or abiraterone acetate treatment. The results showed a clinically meaningful difference in fatigue, favoring abiraterone acetate (3.4 points, $p = 0.003$), while between-group differences in HRQoL measurement were not clinically significant [26].

The real-world phase 4 multicenter study of enzalutamide and abiraterone acetate with prednisone tolerability (REAAcT)

assessed also functional status using the EORTC QLQ-30 and FACIT-Fatigue questionnaires at baseline and 2 months, with 46 patients evaluable for PRO analyses in each of the two treatment groups. Results of the FACIT-Fatigue evaluation demonstrated a statistically significant worsening from baseline in patients taking enzalutamide (−4.00 (95% CI: −6.61 to −1.39)) compared to those receiving abiraterone acetate plus prednisone (−0.01 (95% CI: −2.40 to 2.38)). However, the grade 3/4 adverse events (4% *vs.* 6%) and the overall mean changes from baseline for the EORTC QLQ-C30 assessment were similar in both treatment groups [27].

5. Discussion

Harland's quality of life analysis demonstrated that abiraterone acetate plus prednisone was associated with clinically significant improvements in HRQoL compared with prednisone alone in mCRPC after chemotherapy failure using the FACT-P questionnaire, except for the social/family domains [10]. Analysis of PROs in chemotherapy-naive mCRPC also showed a consistent trend toward a delayed progression of pain and deterioration in scores of individual functional status subscales using the FACT-P instrument in patients treated with abiraterone acetate compared with prednisone alone [13]. El-Amm *et al*. [28] published a review examining the impact of abiraterone acetate therapy on PROs and reported that abiraterone was beneficial in not only prolonging the patients' survival and delaying initiation of chemotherapy but also in delaying HRQoL worsening. Further, analysis of the relationship between HRQoL and disease progression or OS supports the clinical relevance and benefit of HRQoL measures and the rationale for their use alongside the assessment of clinical efficacy indicators in clinical trials and in routine clinical practice [16]. Treatment with enzalutamide in both mCRPC groups (chemotherapy-naive and after chemotherapy failure) demonstrated an association with reduced risk and delayed deterioration in the quality of life and pain progression compared to placebo [17, 18]. Analysis of the relationship between HRQoL and the disease progression or OS in patients treated with enzalutamide confirmed that the baseline status of HRQoL was a prognostic factor for OS and rPFS of mCRPC in chemotherapy-pretreated patients [21].

The results of the AQUARIUS study suggested an advantage of using abiraterone acetate over enzalutamide in preserving cognitive function and fatigue. These differences were observed both at the start of the study and after the initiation of treatment and could be considered when selecting treatment for mCRPC [23]. The Khalaf study, the first to directly compare the efficacy of abiraterone acetate versus enzalutamide in chemotherapy-naive patients with mCRPC using quality of life assessments, suggested that abiraterone acetate had a more favorable impact on HRQoL outcomes based on the FACT-P instrument than enzalutamide in elderly patients [24]. According to the results of the REAACT trial, the overall mean changes from baseline for the EORTC QLQ-C30 assessment were similar in both treatment arms and showed no meaningful change between abiraterone acetate and enzalutamide [27]. Comparatively, the between-group differences in HRQoL outcomes in the Danish HEAT study

were not clinically significant [26].

This systematic review shows that the most commonly used method to assess quality of life is the FACT-P instrument, which was validated for use in mCRPC patients. However, it should be emphasized that FACT-P assessments were performed at different time intervals in different studies, making it difficult to compare the outcomes between the different studies. Some inconsistency was also identified in the definition of the eligible population for HRQoL-related analyses. In the post-chemo trial with abiraterone acetate (COU-AA-301 trial), only patients with impaired HRQoL were included in improvement analyses. To be eligible, patients needed to have a baseline score at or below defined thresholds (*i.e.*, a FACT-P total score ≤122), whereas in the enzalutamide trial (AFFIRM trial), all patients with baseline and post-baseline FACT-P values were eligible for HRQoL improvement analysis [10, 17]. The types of HRQoL assessments based on the FACT-P scale in studies without prior chemotherapy were also different. The pivotal study with abiraterone acetate (COU-AA-302 trial) assessed only the decline in HRQoL, whereas the study with enzalutamide (PREVAIL trial) assessed both improvement and deterioration in functional status [13, 18]. The EQ-5D questionnaire was only used in studies with enzalutamide in chemotherapy-naïve patients. Until now, comparative studies have predominantly assessed cognitive function, depressive symptoms and tolerability of both ARTAs, while only a few head-to-head studies used the FACT-P questionnaire (Khalaf *et al*. [24] and the HEAT study) [26]. Hence, it is difficult to compare the quality of life outcomes of both ARTAs from previous studies, and there is a continued need to verify and directly compare the impact of abiraterone acetate and enzalutamide on the HRQoL of patients in real clinical practice.

6. Conclusion

Abiraterone acetate and enzalutamide have been shown to prolong overall survival and delay mCRPC diseasae progression. Both ARTAs were well-tolerated and demonstrated beneficial effects on quality of life, supporting their use as the standard of care for mCRPC management. While both drugs have also been associated with significant improvements in HRQoL, well-being, and patient functioning, a comparison of outcomes across studies is difficult due to inconsistencies in HRQoL instruments and assessment schedules. As such, there is a continuous need for a direct head-to-head comparison of the impact of abiraterone acetate and enzalutamide on HRQoL in real-world mCRPC patients.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTIONS

MK and JK—Conception and design of work. MK and MB—Literature review. MK—Manuscript draft. JK—Critical re-

vision of the manuscript. All authors revised and edited the important contents of the manuscript, read and approved the final version.

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