Abiraterone plus prednisone or enzalutamide in patients with metastatic castration-resistant prostate cancer: is a question of quality?

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Khalaf et al. (1) presented a sub-sequent analysis of a previously conducted phase II trial aimed to compare activity of abiraterone acetate + prednisone (AA + P) versus enzalutamide (E) in more than 200 patients with treatment-naive metastatic castration-resistant prostate cancer (2). In this study, the authors found that AA + P and E showed similar activity in terms of time to prostate-specific antigen (PSA), clinical, or radiographic progression (2). Based on similar results between the two drugs, the authors focused their subsequent analysis on the secondary end-points of this study related to the patients’ reported outcomes (PROs), i.e., patient-reported health-related quality-of-life (HRQoL), depression and cognitive function, evaluated by patient-completed Functional Assessment of Cancer Therapy—Prostate (FACT-P) quality-of-life questionnaires, Patient Health Questionnaire-9 (PHQ-9) depression symptom questionnaires, and Montreal Cognitive Assessment (MoCA) tests (1). Additionally, a mixed model for repeated measures (MMRM) has been used to compare the change of FACT-P over the time and when there was an interaction between the treatment arm and age, a separate model according age <75 and ≥75 years has been performed. The authors found a positive test for interaction in the treatment arm by age for total FACT-P (P=0.048). However, the change from baseline over time in FACT-P score was better for AA + P then E in the ≥75-year model (P=0.003) while no difference in the <75-year model (P>0.9).

Finally, the authors reported a higher proportion of patients who experienced a worsening for the physical and functional well-being domains in the E arm and the distribution of change in PHQ-9 scores from baseline were in favour of AA + P at different time end points. The authors concluded that the study demonstrated an improvement in patients reported outcomes in men treated with first-line AA + P compared to E. Additionally differences have been observed in the total FACT-P score in the elderly subgroup.

To date, the role of AA + P and E is well established in metastatic castration resistant prostate cancer (3). However, no randomized study has never supported the use of one of the above agents over the other because no direct comparison has been performed in a randomized trial among the two drugs. As consequence, the use of AA + P or E in metastatic castration resistant prostate cancer depend by the different profile of side-effects and on the confidence of the physicians with the drugs.

Patient-reported outcomes are very important in clinical study and in a major way in daily clinical practice (4,5). One of the main adverse events able to reduce the QoL is fatigue (6), Khalaf et al. reported a higher proportion of patients with grade >2 fatigue with E compared with AA + P (39% vs. 20%) (1). Fatigue has been the cause of a dose reduction in the 12% of patients treated with E versus 20% of patients treated with AA + P (1). For this reason, it is reasonable to think that the higher incidence of fatigue with
E may have accounted for the inferior QoL, impairment in daily functioning, depression and anxiety. In line with these data, a meta-analysis of randomized controlled trials from phase III trials of AA + P and E showed an increase in the risk of all-grade fatigue for E (relative-risks of 1.29 versus 0.85 for AA + P) (7). As reported in pivotal trials and additional analyses, both E and AA + P represent suitable options for elderly and frail patients (8). They have been shown to increase overall survival and delay radiographic progression in both post-docetaxel (AFFIRM and COU-AA-301 trials) and chemonaïve (PREVAIL and COU-AA-302 trials) patients (9-12). Moreover, these drugs have been shown a favourable safety profile and a positive impact on QoL. Cella et al. reported QoL data from AFFIRM trial, highlighting that patients treated with E obtained a decrease in HRQoL deterioration as assessed by FACT-P total score and subscales (13). Similar findings were reported in the context of PROSPER trial. E has been shown to be associated with a more favourable health-related QoL outcomes as assessed by FACT-P questionnaires, emotional wellbeing, longer time to clinically meaningful pain progression and symptom worsening than placebo (14).

As far as AA + P, Basch et al. collected PROs from more than 1,000 chemonaïve patients randomly assigned to receive AA + P or placebo in a phase 3 trial (15). They found a benefit in median time to progression of mean pain intensity (26.7 vs. 18.4 months; HR 0.82), median time to progression of pain interference with daily activities (10.3 vs. 7.4 months; HR 0.79) and in median time to HRQoL deterioration based on FACT-P total score (12.7 vs. 8.3 months; HR 0.78) (15).

In treating patients with metastatic prostate cancer outside the context of clinical trials, clinicians must face even more with critical age-related aspects, such as frailty, comorbidities and cognitive and motor Impairment. The patient selection adopted by Khalaf et al. greatly strengthens the results of the study, as it has allowed to enroll a representative population of the routine clinical practice, albeit within a randomized study. Similar results were reported by Thiery-Vuillemin and colleagues in a prospective, observational, non-randomized study (AQUARIUS) (16). Focusing on the first 3 months of treatment, patients receiving E (n=59) experienced more perceived cognitive impairment, fatigue, emotional functioning deterioration, appetite loss and worse cognitive functioning than patients receiving AA + P (n=46). No significantly meaningful differences were observed for pain PRO scales (16).

Another major question regards the role of questionnaires assessing QoL and psychiatric reported outcomes as depression, anxiety and cognitive impairment. Although these tools are widely used in clinical trials, they deserve some consideration. First of all, these questionnaires are mainly patient-based and non-diagnostic. In contrast, a specific psychiatric evaluation is needed to make sure that the patient has cognitive impairment, depression or other mental health conditions. Secondly, these tools, albeit standardized, are often simple collections of symptoms related to the patient’s own perception, but they do not consider the whole state of health and the perceptions of the caregivers (17).

Especially noteworthy is the context in which Khalaf and colleagues set this study. In the last few years, the landscape of metastatic prostate cancer treatment is rapidly changing. Early initiation of AA + P in combination with androgen deprivation therapy (ADT) in patients with hormone sensitive prostate cancer has been recently studied in two clinical trial (LATITUDE and STAMPEDE). The addition of AA + P to ADT has been shown a survival benefit and a prolonged radiographic progression-free survival, resulting in practice changing (18,19).

In addition, basing on PROs reported in the LATITUDE trial, AA + P has been associated with prolonged median time to worst pain intensity progression and median time to worst fatigue intensity, as well as lengthened median time to deterioration of functional status (20).

However, we should report important limitations in the study by Khalaf et al. such as the limited number of patients enrolled that preclude from definitive conclusions as reported by the authors: “statistical analyses were not prespecified and we did not correct for multiple comparisons.” (1).

In conclusion, toxicity profile remains one of the main elements of treatment choice, while waiting for reliable predictive response factors. Since these treatments will be used for an even greater length of time, safety aspects deserve specific attention. For this reason, further studies are expected to help clinicians select treatment based on the toxicity profile of each drug.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest.

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References


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