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Commentary

Predictive biomarkers of response are required for the evaluation of patients with metastatic castration-resistant prostate cancer treated with a sequential regimen

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Schrader *et al* analyzed the effects of the sequential regimen, Abiraterone Acetate (AA) followed by Enzalutamide (E). Their data showed that E is only moderately effective after AA failure. However, a significant biochemical response (>50% PSA decline) to E was observed only in some patients who had previously achieved a >50% PSA decline with AA treatment. Then, cross-resistance between AA and E seems to be a common event and in some cases OS achieved in patients after Docetaxel failure is even longer when they are treated with AA or E only rather than when a sequential strategy with these two agents is undertaken. However, a subset of these patients who underwent a sequential therapy has shown benefits in terms of OS. Therefore, the development of predictive biomarkers of response is required in order to tailor the new therapeutic agents to the biology of the cancer and to obtain max OS.

Keywords: Abiraterone Acetate, Enzalutamide, Sequential regimen, Cross-resistance

INTRODUCTION

Schrader *et al* 2013, analyzed the effects of the sequential regimen, AA followed by E. Their data showed that E is only moderately effective after AA failure. Of the 35 patients in this study, 25 (71.5%) did not respond to subsequent E therapy with a PSA decrease > 50%. The median overall survival (OS) was 7.1 months, after median duration of prior AA of 9 months. The sum of AA treatment duration and OS since starting treatment with E was of 16.1 months, after failure of D first-line chemotherapy. However, a significant biochemical response (>50% PSA decline) to E was observed only in 7 of the 16 patients who had previously achieved a >50% PSA decline with AA treatment. These patients' OS after

failure of D first-line chemotherapy was 21.9 months.

In 2012, Fizazi *et al.* showed that AA prolonged OS (15.8 months vs 11.2 months) in metastatic castration-resistant prostate cancer (mCRPC) patients after D failure and median treatment duration was 7.4 months. Comparing this study with the one by Schrader *et al.*, we can observe that the reported OS in the latter is similar to the one reported in the study Fizazi *et al.* in which AA after D failure was the only used regimen. Nonetheless, a subset of patients described by Schrader, who responded to AA and E, achieved an OS of 21.9 months, hence longer than the 15.8 months OS of the patients treated with AA only reported by Fizazi *et al.* Comparing these

last two studies we can highlight conflicting data which may arise doubts and questions in those oncologists who treat CRPC. Indeed, cross-resistance between AA and E seems to be a common event and in some cases OS achieved in patients after D failure is even longer when they are treated with AA or E only rather than when a sequential strategy with these two agents is undertaken. However, a subset of these patients who underwent a sequential therapy has shown benefits in terms of OS. Therefore, the development of predictive biomarkers of response is required in order to tailor the new therapeutic agents to the biology of the cancer and to obtain max OS. In addition, further investigations should evaluate AA clinical activity after E progression and vice versa. These trials should also define if the potential cross-resistance between AA and E impacts the most suitable treatment sequence for these drugs in CRPC patients and help physicians designing the best individual therapeutic strategy.

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