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Determining the Optimal Treatment for Metastatic Castration-resistant Prostate Cancer: Age Should Not Be a Factor

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In the current issue of *European Urology*, Mulder and colleagues report the results of a post hoc subgroup analysis of the COU-AA-301 (postdocetaxel) study focusing on the efficacy and safety of abiraterone in elderly patients (>75 yr of age) [1]. Although overall survival by subgroups was already presented in the final survival analysis of the study [2], these additional data confirm the relative efficacy and safety of abiraterone/prednisone exposure versus placebo/ prednisone in elderly patients. In this trial, 28% of the overall study population was 75 yr or older, allowing analysis of the interaction between age and abiraterone therapy.

Treatment with abiraterone acetate yielded improved survival across the two age cohorts. The elderly (>75 yr) subgroup demonstrated hazard ratios (HRs) for death (HR: 0.64; 95% confidence interval [CI], 0.48–0.85) at least equivalent to younger patients (HR: 0.78; 95% CI, 0.65–0.93). This finding is perhaps unsurprising because multiple trials in this setting have demonstrated similar survival benefits for several active agents in older men with metastatic castration-resistant prostate cancer (mCRPC). For example, post hoc analysis of the AFFIRM trial of enzalutamide demonstrated similar benefit in both older and younger subgroups [3]. Subgroup analysis of the TAX327 study of every 3 wk docetaxel demonstrated similar HRs for overall survival in elderly men using age cutoffs of 69 and 75 yr (HRs: 0.77 and 0.80, respectively, vs 0.81 for younger patients) [4]. A large retrospective study evaluating docetaxel therapy in the elderly in a real-world setting found that elderly patients with a good Eastern Cooperative Oncology Group performance status (PS) responded similarly to younger patients, although unsurprisingly those with a poor PS tolerated docetaxel quite poorly [5]. Because most patients in the COU-AA-301 study had a favorable PS, the relative benefit of this compound in a group of men with advanced age, significant comorbidities, and limited performance status cannot be determined. The extensive experience in mCRPC with various compounds (cytotoxic, radiopharmaceutical, and endocrine drugs) supports that age alone does not reduce the chances of benefit from systemic treatment.

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Previous concerns have been raised regarding the potential for increased toxicity in the elderly with the potential for polypharmacy/drug interactions and cardiac toxicity given abiraterone's potential for causing mineralo-corticoid excess. The data presented here are largely reassuring on that front, although there was a slightly increased incidence of atrial fibrillation and tachycardia in the elderly treated group, a difference not seen in the younger treated group. Treatment-emergent cardiac events leading to death were seen in only 2% of the elderly treated group versus 1% in the placebo group and 1% in the younger group. Additional follow-up of the COU-AA-302 study will further define the safety of abiraterone as the duration of drug exposure lengthens.

An important consideration is that the population of elderly patients presented in this report is highly selected given that they maintained a PS 2, recovered from docetaxel without major functional and medical impairment, and were selected to exclude preexisting cardiac ailments. Extrapolation of the safety of abiraterone to a real-world elderly population should thus be performed with caution. Nevertheless, this study does provide additional evidence that age should not be the major consideration in the choice of therapy and that in elderly men (who were not previously treated with abiraterone, enzalutamide, or ketoconazole) progressing on docetaxel, abiraterone may yield a safety profile that, historically, appears more favorable than other more toxic treatments such as cabazitaxel, for example.

The analysis presented here is of course limited in that it is a post hoc subgroup analysis and thus hypothesis generating. A further limitation is the question of the dichotomization at age 75, which appears arbitrary; a statistical or clinical justification for this cut point, although reasonable, is not provided in the article.

The COU-AA-301 study served to satisfy the Food and Drug Administration regulatory framework by demonstrating a survival benefit with abiraterone when given after docetaxel. The number of therapeutic options for patients with mCRPC is growing rapidly. However, the optimal sequencing of these agents in clinical practice remains elusive at this time. Drug approval strategies, as in the case of abiraterone acetate, enzalutamide, radium-223, sipuleucel-T, and cabazitaxel, are often linked to regulatory requirements. Trials are designed to include only selected patient populations, especially in terms of prior treatment and other disease and host characteristics (eg, excellent PS and no significant comorbidities) to optimize conditions to test their hypothesis with minimal interference of confounding factors.

Consequently, extrapolation of data from pivotal trials should be done cautiously because they may not represent the real-world clinical practice environment. This can be illustrated by the postapproval preliminary experience reported in patients treated with enzalutamide in the postdocetaxel space who were previously treated with abiraterone [6]. The authors reported >50% decline in prostate-specific antigen (PSA) in only 10 of 35 patients (28.6%) with a median duration of enzalutamide treatment in all patients of only 4.9 mo and a median survival of 7.1 mo. This is in contrast to the experience reported in the pivotal trial reported by Scher et al. in patients previously treated with docetaxel but not abiraterone where the authors reported 54% of men with >50% decline in PSA, 8.3 mo of median time to PSA and radiologic progression, and a median survival of 18.6 mo [7].

A study of 30 men who progressed on enzalutamide (having previously progressed on docetaxel) in the AFFIRM trial and who then went on to receive abiraterone preliminarily demonstrated no radiographic response and a median time to progression of only 3.8 mo [8]. Similarly, in a separate report by Mezynski et al., mCRPC patients progressing through abiraterone had fewer and less durable responses to docetaxel (metastatic progression-free survival: 4.6 mo) than historical controls. Further, there was 100% concordance between men who were abiraterone and docetaxel refractory, which led the authors to suggest cross-resistance due to a putative androgen receptor–mediated mechanism of action for docetaxel [9].

Given the evidence suggesting that both abiraterone and enzalutamide increase the expression of androgen-receptor variants (AR-Vs), which appear to mediate a component of AR-targeted therapy resistance [10], the efficacy of sequential therapy with these agents may be quite limited. Ultimately, novel therapies in this setting that are able to target these AR-Vs may be most effective after progression.

Evolving data with AR-targeted therapies and the autologous immunotherapy sipuleucel-T further illustrate potential interactions between treatments that as single agents have a significant survival benefit in mCRPC. Preclinical and preliminary clinical information is intriguing because augmentation of the cytokine response in biochemically recurrent patients receiving androgen-deprivation therapy first followed by sipuleucel-T was observed, whereas the reciprocal did not demonstrate augmentation [11]. A small phase 2 study of sipuleucel-T with either concurrent or sequential abiraterone demonstrated similar immunologic profiles [12]. The timing of sipuleucel-T therapy and potent AR-targeted therapies is thus of interest, with larger randomized studies needed. Radium-223 has also demonstrated improved overall survival with relatively minimal hematologic toxicity in men with CRPC and bone but no visceral metastases [13]. Given that it appears to be very well tolerated and without significant risk for drug interactions, the combination or sequencing with other active agents remains an important open question.

The reported analysis of the COU-AA-301 trial highlights several key issues in CRPC. First, the description of benefits and toxicities of patient subsets may help clinicians and patients in their choice of treatment among the several options now available. However, given the stringent selection criteria for participants in large pivotal randomized trials, extrapolation of clinical data to a real-world setting should be done carefully, particularly in light of questions regarding sequencing of therapies and potential interactions and cross-resistance mechanisms among available active therapies. Ultimately, optimal treatment selection may depend more on molecular characterization and genotyping (eg, of AR-Vs) than on clinical factors such as age.

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