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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Enzalutamide in chemo-naïve castration-resistant prostate cancer: effective for most but not for all

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Continued research in the treatment of castration-resistant prostate cancer (CRPC) has allowed for a clearer understanding of this disease entity and further treatment advances. In a study recently published by Beer *et al.*[1] in the *New England Journal of Medicine*, another advance to treatment was demonstrated for the androgen receptor (AR) signaling inhibitor, enzalutamide, in patients with chemotherapy-naïve metastatic CRPC. Although a large majority of patients responded favorably to enzalutamide in the prechemotherapy setting, a small but significant proportion of patients demonstrated no meaningful benefit to this agent. This highlights an important concept in the understanding of this disease: inherent and acquired resistance to AR-targeting therapies.

With a recent re-emphasis on the AR and androgen signaling, multiple therapeutic approaches have emerged for the treatment of CRPC. The most notable of these modalities are the androgen synthesis inhibitor abiraterone (currently Food and Drug Administration (FDA) approved for patients with metastatic CRPC both before and after chemotherapy treatment) and the AR signaling inhibitor enzalutamide (currently FDA approved for metastatic CRPC patients who have received prior chemotherapy).

In the recently published PREVAIL study, Beer *et al.*[1] evaluated the clinical efficacy of enzalutamide in men with chemotherapy-naïve metastatic CRPC. Patients were equally randomized into two treatment arms of either placebo or enzalutamide and were monitored in a blinded fashion, with the co-primary endpoints being progression-free survival (PFS) and overall survival (OS). Unlike the prechemotherapy abiraterone study (COU-AA-302),[2] patients with visceral metastasis were allowed to enroll. As reported by the authors, the enzalutamide-treated group had a 65% PFS rate at 12 months compared with 14% in the placebo-treated group (relative risk reduction of 81%). Moreover, treatment with enzalutamide translated into a small but significant median OS benefit over placebo (32.4 *vs* 30.2 months, relative risk reduction of 29%). Enzalutamide also produced additional clinical benefits including prolonging skeletal-related events and delaying the need for chemotherapy. These findings broadly parallel those of abiraterone in the prechemotherapy COU-AA-302 trial,[2] providing additional evidence that continued ablation of the androgen-AR axis can provide clinically meaningful benefits to many patients with metastatic CRPC.

However, a sobering reality is that a significant proportion of CRPC patients do not show any treatment responses to enzalutamide (or abiraterone). In the PREVAIL study, 9% of men receiving enzalutamide experienced a prostate specific antigen (PSA) increase as their best response (this can be compared to the postchemotherapy AFFIRM study,[3] where 21% of enzalutamide-treated men had a PSA increase as their best response). These patients can be considered to have primary refractory disease to enzalutamide. In such patients, treatment with enzalutamide only delayed the time to initiating appropriate therapy. However, clinical biomarkers to prospectively identify men who might demonstrate primary resistance to enzalutamide are currently lacking. This highlights the need for a better understanding of treatment resistance mechanisms in order to appropriately manage our patients. Ideally by knowing disease mechanisms of resistance, biomarkers can be developed to predict which patients are likely to respond to therapy and, therefore, guide treatment decisions in a rational manner.

There are several hypothesized or documented mechanisms of resistance to enzalutamide and other AR-directed therapies. Most of the knowledge in this area comes from cell line experiments and xenograft models of CRPC, while some clinical data is also beginning to emerge. These postulated pathways of enzalutamide (and abiraterone) resistance include aberrations in androgen-AR signaling such as overexpression of the AR,[4] *de novo* synthesis of androgens,[5] nonspecific ligand-binding to the AR,[6] activating mutations in the ligand-binding domain of the AR,[7] and the generation of alternatively-spliced AR transcriptional variants.[8] Other resistance mechanisms include overexpression of the glucocorticoid receptor,[9] and upregulation of alternately oncogenic pathways such as reciprocal activation of PI3K/AKT signaling.[10] There is also on-going work evaluating the altered expression or mutation of DNA expression factors such as co-repressors or co-stimulatory DNA binding elements, as well as other possible epigenetic and genetic changes.[11]

Our group has recently focused on blood-based detection of AR splice variants, specifically AR-V7, from circulating tumor cells (CTCs) of patients embarking on therapy with enzalutamide and abiraterone.[12] In a very heterogeneous population of 62 enzalutamide- or abiraterone-treated patients, we identified AR-V7 in baseline CTC samples from 29% of such patients. Notably, none of the AR-V7-positive patients achieved a PSA response to enzalutamide or abiraterone, suggesting that this may be one

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possible marker of primary resistance to both agents. Interestingly, the prevalence of AR-V7 in men with enzalutamide- and abiraterone-naïve CRPC from this analysis was 11%, while this rate increased in men that had previously received one or both agents. This proportion (11%) parallels the proportion of men without any PSA decline to enzalutamide in the PREVAIL study (9%), potentially implying that presence of CTC-derived AR-V7 might be the predominant mechanism of resistance to enzalutamide in these men.

One challenge in the molecular biology of CRPC is to identify the driver mutations from all of the passenger mutations, thereby focusing treatment on the critical pathways. For example, it has been argued that *de novo* steroidogenesis is less important than other factors in the progression of CRPC.[13] It has also been suggested that AR splice variants may not necessarily drive resistance to AR-targeting therapies, because splice variants always co-exist (and often heterodimerize) with wild-type AR.[14] However, laboratory results do not always mirror clinical data. Adding further to this complexity is the intrinsic heterogeneity of CRPC tumors and the continued evolution with new mutations developing over time and in response to prior therapies. Some of these evolving mutations also appear to induce cross-resistance to future treatments, although the molecular basis of this has not yet been fully determined. For example, at least one study has suggested that docetaxel may prove less efficacious after patients have previously received potent AR-directed therapies.[15] It is also clear that AR-directed therapies are less effective after docetaxel has been administered, as evidenced by the inferior PSA response rates, objective tumor response rates, and shorter PFS and OS observed with enzalutamide in the postdocetaxel setting (AFFIRM) compared to the predocetaxel setting (PREVAIL). With many treatment options available and more currently in development, it is critical to know how to best sequence and combine our therapies so that patients can maximally benefit.

In conclusion, the PREVAIL trial highlights a successive improvement in the treatment of patients with metastatic CRPC, with definite benefits observed in clinically relevant outcomes such as PFS and OS. However, the more important lesson learned from this trial is the need to prospectively identify patient cohorts that will not respond to therapy by better understanding disease resistance mechanisms, and targeting these patients with alternative or novel therapies.

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