Steroid Sidestep: Evading Androgen Ablation by Abiraterone

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Tumor mechanisms of abiraterone resistance in clinical prostate cancer are not well defined. Chen and colleagues report that a T878A androgen receptor mutation occurs in a subset of patients progressing while receiving abiraterone, suggesting that this may be a therapeutically exploitable mechanism of abiraterone resistance in castration-resistant prostate cancer. Clin Cancer Res; 21(6); 1240–2. ©2014 AACR.

The report by Chen and colleagues sheds new light on resistance to abiraterone and is spurred in part by two observations. First, CYP17A1 inhibition with abiraterone deflects steroid synthesis away from pathways resulting in 19-carbon steroids (i.e., androgens) and toward those that produce 21-carbon steroids (8), including a 4- or 5-fold increase in tissue progesterone concentrations (9). Second, the AR T878A mutation present in the LNCaP human cell line model of prostate cancer has broadened specificity such that progesterone functions as an AR agonist, and may drive tumor progression by way of this mechanism (10).

In this issue of Clinical Cancer Research, a study by Chen and colleagues (1) provides a mechanistic insight into clinical resistance to abiraterone, which may lead to new strategies for the treatment of prostate cancer. Treatment of advanced prostate cancer with gonadal testosterone deprivation therapy (i.e., medical or surgical castration) eventually leads to the development of castration-resistant prostate cancer (CRPC), which evolves because tumors develop the capability to synthesize their own testosterone and/or dihydrotestosterone from precursors, as well as other mechanisms of stimulating the androgen receptor (AR; refs. 2 and 3). Synthesis of androgens requires 17α-hydroxylase/17,20-lyase (CYP17A1), an enzyme that demonstrates robust activity in the human testes, adrenal gland, and possibly some CRPC tissues. In the castrate setting, the human adrenal gland is the major producer of metabolites downstream of CYP17A1, largely in the form of dehydroepiandrosterone (DHEA) and DHEA-sulfate. CRPC converts these and other precursors to testosterone and/or dihydrotestosterone, which stimulate the AR (4).

Abiraterone (administered orally as abiraterone acetate) potently inhibits CYP17A1 enzymatic activity, depletes serum adrenal androgens (DHEA, DHEA-sulfate, and other less-abundant androgens), induces clinical responses, and prolongs survival for patients with metastatic CRPC (5, 6). Although abiraterone represents a significant therapeutic advance, tumors ultimately become resistant and progress. Furthermore, abiraterone-resistant tumors are also frequently resistant to subsequent treatment with enzalutamide, a recently developed AR antagonist that otherwise confers a survival benefit (7). The increasing evidence of clinically relevant cross-resistance between abiraterone and enzalutamide may not be surprising, particularly given that both agents intervene along the androgen/AR signaling axis, although the mechanisms of these agents are distinct. Nonetheless, tumor mechanisms of resistance to these agents are not yet well defined.

In the same population that was enriched with this combination of drugs, Chen and colleagues report that a T878A androgen receptor mutation is detectable in a subset of patients progressing while receiving abiraterone, suggesting that this may be a therapeutically exploitable mechanism of abiraterone resistance in CRPC (7). The increasing evidence of clinically relevant cross-resistance between abiraterone and enzalutamide may not be surprising, particularly given that both agents intervene along the androgen/AR signaling axis, although the mechanisms of these agents are distinct. Nonetheless, tumor mechanisms of resistance to these agents are not yet well defined.

In this study, Chen and colleagues performed a genome-wide analysis of genomic DNA obtained from 18 tumors progressing on pharmacologic combination with daily dutasteride (3.5 mg) and prednisone (5 mg). Of 18 patients, 3 had the AR T878A mutation detectable in progressing tumors. These 3 patients included the patient treated with ketoconazole (67.7% of AR mRNA reads), 1 patient treated with abiraterone alone (60.3% of AR mRNA reads), and 1 patient treated with abiraterone, dutasteride, and prednisone (6.0% and 18.4% of AR mRNA reads from 2 liver biopsies). In tissue obtained prior to therapy from a liver lesion in the patient treated with abiraterone, dutasteride, and prednisone, 0.09% of AR mRNA reads showed the T878A mutation, suggesting that this mutation preexisted at a low frequency and represented a cell population that was enriched with this combination of drugs. Analysis of genomic DNA obtained from these tumors confirmed these findings. None of the patients found to have this mutation had been previously treated with flutamide or nilutamide—agents that are known to function as agonists in the presence of the mutation. In addition to the analyses done in tumors from patients with metastatic CRPC, the AR T878A mutation was also found in a focus of localized prostate cancer that persisted after treatment in a neoadjuvant study of castration plus abiraterone for 24 weeks, before radical prostatectomy (9), suggesting that earlier emergence of this mutation may occur when abiraterone is combined with upfront castration.

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The lower frequency of the AR T878A mutation in patients treated with the combination of abiraterone, dutasteride, and prednisone (1 of 14), as compared with abiraterone alone, might indicate that dutasteride and/or prednisone inhibits enrichment of mutation-bearing tumor cells. Although suggestive, the number of patients in each group is small and not enough for a definitive comparison. Notably, glucocorticoids (including prednisone), which are usually administered with abiraterone to suppress mineralocorticoid excess, may also suppress abiraterone-mediated progesterone upregulation (11). Furthermore, as the authors point out, it is possible that selection for the AR T878A mutation is not directly due to progesterone and is instead driven by another 21-carbon steroid that serves as an AR agonist in this context.

The most important clinical implication of these findings from Chen and colleagues is that this study seems to have identified a therapeutically exploitable mechanism of abiraterone resistance. Enzalutamide is effective in blocking the AR T878A-mutant AR and abiraterone-resistant tumor progression. The use of glucocorticoids while remaining on abiraterone treatment (13), or responses in patients who switch to an alternative glucocorticoid (14)? Do patients with tumors driven by the AR T878A mutation represent the slim proportion of those who respond to enzalutamide after the development of abiraterone resistance (7)? This should be a high-priority question that investigators in the field can and should answer. Is selection for the population of tumor cells with the AR T878A mutation maintained upon abiraterone discontinuation and consequent progesterone suppression? If not, should patients with tumors that harbor this mutation be maintained on abiraterone to accentuate any response to enzalutamide? Finally, if adding dutasteride and/or prednisone to abiraterone suppresses the emergence of a dominant clone with the AR T878A mutation, is this really a desirable effect? Would it not be better to shepherd the tumor toward molecular mechanisms of abiraterone resistance that are potentially therapeutically exploitable? Chen and colleagues (1) should be commended for their study, which should serve as a starting point for understanding nonoverlapping mechanisms of clinical cross-resistance between abiraterone and enzalutamide and an entryway to therapeutic clinical studies.

**Disclosure of Potential Conflicts of Interest**
N. Shariati reports receiving a commercial research grant from Janssen and is a consultant/advisory board member for Medivation, Sanofi, and Janssen.

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**Figure 1.**
Simplified schema of progesterone stimulation of the AR T878A mutation in abiraterone-resistant prostate cancer. A, CYP17A1 is required for androgen synthesis and wild-type AR-dependent tumor progression and leads to an increase in progesterone synthesis. B, abiraterone blocks androgen synthesis and wild-type AR-dependent tumor progression. C, progesterone stimulates the T878A-mutant AR and abiraterone-resistant tumor progression.

- **A**
  - Pregnenolone → Progesterone
  - CYP17A1
  - Tumor progression
  - Androgens → Wild-type androgen receptor
- **B**
  - Pregnenolone → Progesterone
  - CYP17A1
  - Tumor progression
  - Androgens → Wild-type androgen receptor
- **C**
  - Pregnenolone → Progesterone
  - T878A
  - Androgen receptor
  - Tumor progression
  - Androgens → Wild-type androgen receptor

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