Can Targeting the Androgen Receptor in Localized Prostate Cancer Provide Insights Into Why Men With Metastatic Castration-Resistant Prostate Cancer Die?

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The improved survival observed with abiraterone acetate\(^1\,^2\) or enzalutamide\(^3\,^4\) in patients with metastatic castration-resistant prostate cancer (mCRPC) who experience disease progression despite conventional androgen-deprivation therapy (ADT) validates the androgen receptor (AR) as a viable target in this group of patients. Yet many questions remain, particularly in light of the so-called bookends of the published clinical data that lead to the approval of these drugs. On one end of the spectrum, the fairly remarkable success that has been observed with these agents has been paired with the equally sobering realization that the development of resistance to these agents is nearly universal and is often associated with the development of a highly aggressive phenotype with rapidly progressive, fatal disease, for which few viable therapeutic options exist. At the other end of the spectrum, investigators have been pushing the envelope to use these active agents in earlier disease states, where disease burden is lower, patients are less heavily pretreated, and potentially, a broader therapeutic index can be exploited. In the article that accompanies this editorial, Taplin et al\(^5\) report the results of a phase II clinical trial of preprostatectomy (neoadjuvant) abiraterone acetate. Although the results of this trial do not support the use of this approach as a standard of care, they provide important insights into the questions at both ends of the therapeutic spectrum.

For many cancer types, the development of systemic therapy for high-risk localized disease has been predicated on a potential impact on both local and micrometastatic disease control. In the case of localized prostate cancer, there is every reason to believe that neoadjuvant ADT should be of utility. First, a cohort of patients with a high risk of recurrence can be readily identified,\(^6\,^7\) so enrichment strategies that result in a more robust activity signal can be developed. Second, oncogenesis and disease progression is deeply dependent on a single signaling pathway, the AR, with the vast majority of cancers relying on this pathway for growth and survival. Third, the pathway can be effectively and easily pharmacologically targeted. Fourth, there is ample evidence that inhibition of the specific pathway is sufficient to halt the neoplastic phenotype. Finally, this approach has been extensively tested and validated in patients with advanced disease, for whom ADT is the standard of care, and widely used because of its significant palliative and life-prolonging effects. On the basis of these observations, the utility of neoadjuvant (preprostatectomy) ADT has been extensively explored.\(^8\,\ldots\,^1^5\) Surprisingly, although several series demonstrated a reduction in the rate of positive surgical margins, in no patient has this observation translated into an improvement in prostate-specific antigen (PSA) –progression-free survival, a generally accepted intermediate outcome end point,\(^5\) nor has a survival advantage been demonstrated for this approach. Consequently, neoadjuvant ADT is neither widely used nor recommended in treatment guidelines and algorithms, with National Comprehensive Cancer Network guidelines specifically indicating that, "Neoadjuvant ADT for RP [radical prostatectomy] is strongly discouraged."\(^1^6\,^9\)

Why has neoadjuvant ADT failed to demonstrate clinical benefit in patients with localized prostate cancer? It is possible that localized prostate cancer is simply not as uniformly and exquisitely dependent on androgens as mediators of transcriptional activity as anticipated. Stated another way, there might exist prostate cancer cells, even at this early stage of disease, that are resistant to ADT. Whether such resistance is innate or adaptive in response to the selective pressure of therapy is an important and unresolved question. Alternatively, it has been postulated that the problem lies not in a lack of sensitivity to ADT, but rather in inadequate androgen deprivation itself.\(^1^7\) These hypotheses can each be tested. The former—that there exist clones of cells that are not sensitive to ADT—is being prospectively tested by the Cancer and Leukemia Group B (CALGB [Alliance]) study 90203, an intergroup trial randomly assigning men with high-risk localized prostate cancer to neoadjuvant ADT plus docetaxel followed by radical prostatectomy versus immediate prostatectomy with no neoadjuvant therapy.\(^1^8\) The second premise: that conventional ADT is inadequate and results in incomplete tissue suppression of androgens, which in turn results in incomplete tumor killing, is the hypothesis addressed by Taplin et al.\(^5\) This hypothesis was put forth by Mostaghel et al,\(^1^7\) who had previously demonstrated that so-called standard ADT inadequately suppressed androgen-regulated gene expression, and suggested that ablation or reduction of circulating androgens was not necessarily reflective of androgen ablation within the prostate itself.
Taplin et al turned to abiraterone acetate as a means of achieving more intense androgen deprivation in the neoadjuvant setting. Abiraterone acetate prolongs survival in patients with mCRPC, and therefore seems to be an appropriate agent to test in earlier stages of the disease. Abiraterone acetate is a prodrug for abiraterone, a CYP17 inhibitor, which has the capacity to lower serum testosterone levels to less than 1 ng/dL (compared with levels closer to 20 ng/dL that are achieved with conventional ADT). The premise that underpinned the use of abiraterone in this trial was that it would decrease intraprostatic androgen levels, which would translate to decreased AR transcriptional activity, and in turn to clinical benefit. Patients with intermediate- to high-risk localized prostate cancer were randomly assigned to 12 weeks of systemic ADT (with a luteinizing hormone-releasing hormone agonist [LHRHa]) alone, or with the addition of abiraterone, before measuring tissue androgen levels in biopsies. Subsequently, all patients received an additional 12 weeks of combination LHRHa plus abiraterone therapy before undergoing radical prostatectomy. This approach allowed two comparisons: the primary planned analysis comparing two concurrently treated, randomly assigned cohorts, and a sequential cohort in which every patient who started out on LHRHa alone served as his own control when he underwent cross-over and abiraterone was added to his regimen. The primary end point of this study was pharmacodynamic—the impact (at 12 weeks) on tissue levels of testosterone and dihydrotestosterone. Notably, the randomized and sequential data regarding hormone levels were internally consistent, providing confidence in the data, and furthermore suggesting that in the future, biopsies to determine tissue hormone levels can be used in lieu of full prostatectomy specimens. It is important to note that this study was not designed to test the clinical benefit of this approach, nor was it powered to detect differences in clinical or pathologic outcomes. In addition, the use of a cross-over design confounds the pathologic data, which reflect either 12 or 24 weeks of abiraterone, but does not allow a comparison with a control group of patients receiving no abiraterone therapy.

The study met its primary goal, in that the addition of abiraterone acetate to LHRHAs, whether evaluated as part of the randomized design of the trial or as the cross-over design, resulted in deeper suppression of androgen levels. Relative to LHRHa alone, the addition of abiraterone resulted in an 85% decline in dihydrotestosterone (DHT) levels, a 97% to 98% decline in dehydroepiandrosterone (DHEA) levels, and a 77% to 78% decline in androstenedione levels. Interestingly, testosterone tissue levels decreased only half as much as DHEA levels, and a 97% to 98% decline in androstenedione levels. The presence of AR-nonresponsive tissue, in which AR androgen receptor (AR) binding parallels AR transcriptional activity, suggests that the presence of AR-responsive tissue (using nuclear AR staining and PSA staining as putative markers of AR responsiveness) might argue that the presence of resistant cancer simply reflects inadequate therapy and the need to further optimize the type and duration of neoadjuvant therapy. By contrast, the presence of AR-nonresponsive tissue, in which AR and...
PSA staining were abrogated, would argue for a non-AR–mediated mechanism, either intrinsic to the cancer or acquired (adaptive) within 24 weeks of therapy. The data are complex. If abrogation of PSA or AR expression is arbitrarily defined as staining that is either absent or involving less than 10% of cells, it is clear that AR and PSA do not track together. There is more AR abrogation than there is PSA abrogation, with nuclear AR staining abrogation in approximately 6% of patients with residual cancer, cytoplasmic AR abrogation in approximately 25% of patients, and more broad PSA abrogation in approximately 75% of patients with residual cancer. Interestingly, the distribution of AR and PSA staining was similar between treatment groups, and it is clear that populations of AR-positive and -negative and/or PSA-positive and -negative cells can coexist within the same patient. Resistant disease with AR pathway abrogation seems to occur in a minority of patients but raises an important question with broad therapeutic implications. Is there a preexistent abiraterone-refractory clone of cells, or does abiraterone-refractory disease arise as a consequence of an adaptive response to exposure to abiraterone?

In summary, targeting the AR in the preprostatectomy setting with abiraterone acetate has a clear biologic effect, decreasing tissue levels of androgens as well as serum PSA levels. However, this effect has not yet been shown to translate into clinical benefit and cannot be considered a standard of care. The early emergence of resistance may in part reflect a pharmacokinetic or pharmacodynamic impediment but may also reflect the emergence of non-AR–mediated resistance to abiraterone. Whether these mechanism(s) are innate or adaptive, and whether the same process is responsible for abiraterone resistance in patients with metastatic CRPC, are important and as yet unanswered questions. The work from Taplin et al5 is an important contribution toward answering these questions.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Editorial
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