

First-Line Use of Novel Hormonal Agents in Prostate Cancer: A Critical Appraisal

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Abstract: Castration has been the hallmark of the treatment of advanced prostate cancer for nearly a century. Conventional surgical or medical castration for the management of metastatic prostate cancer has been associated with an initial response rate greater than 60% to 70%, depending on the criteria employed. The median duration of the initial response is usually less than 3 to 5 years, however, depending on the extent of disease. The failure of disease to respond to castration has been associated with an increase in the production of adrenal androgens and/or the evolution of upregulated or mutated androgen receptors. Second-line hormonal treatment with adrenal inhibitors is sometimes used, but remissions usually last for less than a year. Extensive translational research has produced a series of second-line, multitargeted, hormonally active agents that inhibit androgen receptor function and/or multiple sites within the hypothalamic/pituitary/end-organ axis. Abiraterone and enzalutamide have been shown to be active in second-line or subsequent hormonal therapy for castration-resistant prostate cancer, and recent data have shown a substantial anticancer effect in initial therapy. The potential use of abiraterone and enzalutamide as initial therapy for advanced prostate cancer is the focus of this brief review, which emphasizes that new approaches should not become the standard of care until they have been validated in randomized trials. In addition, it remains unclear whether first-line treatment with chemohormones or new-generation hormones should be the current standard for all patients with newly diagnosed metastatic prostate cancer.

Introduction

For nearly a century, it has been known that advanced prostate cancers are driven predominantly by androgens—which arise mainly from the testes or adrenals—and that the majority of prostate cancers can be controlled with medical or surgical castration, often for a period measured in years.^{1,2} However, relapse occurs in most patients who have metastatic prostate cancer within 5 years after treatment initiation. The physiology involves interplay between components

Keywords

Abiraterone, androgen receptor, AR-V7, castration-resistant, enzalutamide, hormone-naïve, LHRH, metastases, prostate cancer, PSA

of the hypothalamic/pituitary/end-organ axis, which consists of well-characterized feedback loops.² The entry of androgens into prostate tissues is governed by androgen receptors,³ and it has been demonstrated that these receptors are often upregulated or mutated after prolonged exposure to the castration environment. Prostatic tumors with significant neuroendocrine elements are usually resistant to this physiologic construct⁴ and are not covered in this article.

An extensive set of randomized trials has identified the optimal way of achieving medical castration. Specifically, it has been shown that the combination of androgen blockade by means of medical castration with luteinizing hormone–releasing hormone (LHRH) agonists plus peripheral blockade is more effective than LHRH agonists alone⁵; however, it is less clear whether surgical castration plus peripheral blockade provides the same advantage.^{6,7} Continuous medical castration has been shown to be somewhat more effective than intermittent therapy, although the difference is modest.⁸ It also appears that immediate castration for men with asymptomatic metastatic disease does not necessarily afford a survival benefit when compared with delayed treatment if applied judiciously.⁹

Second-Line Hormonal Therapy in Metastatic Castration-Resistant Prostate Cancer

Adrenal androgens are associated with relapse or progression after first-line castration therapy.² Although their activity is attenuated compared with that of testicular androgens, they are able to enter prostate tissue via androgen receptors, in a manner analogous to the passage of dihydrotestosterone into these cells. In the castration environment, the androgen receptors are upregulated or mutated, so that the entry or effect of adrenal androgens in prostatic tissues is increased. In addition, androgen biosynthesis enzymes are upregulated.¹⁰

Agents that inhibit the function of the adrenal gland to reduce levels of the key adrenal androgens, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S), can be used to bring relapsed prostate cancer under control, although the duration of the effect is usually modest.¹¹ In the 1980s, aminoglutethimide was the standard salvage treatment after failure of castration, with subjective and objective response rates of approximately 20% to 30%.¹¹ It was taken off the market, however, allegedly because of a lack of profitability for its manufacturer. It was supplanted in this role by the antifungal agent ketoconazole, which had been shown to have an unexpected toxic effect of suppressing adrenal and testicular androgens by inhibiting cytochrome P-450 14 α -demethylase, an enzyme that converts lanosterol to cholesterol (part of the androgen biosynthesis pathway).²

Early-phase trials showed that 20% to 75% of relapsed prostate cancers responded to this agent, with a median duration of response of less than 12 months.²

Novel Hormonal Agents for the Salvage Treatment of Prostate Cancer

More recently, an extensive program of pharmaceutical research has identified agents, such as abiraterone acetate (Zytiga, Janssen Biotech), that interfere with the androgen axis by inhibiting another cytochrome P-450 enzyme, CYP17, involved in androgen biosynthesis. Extensive phase 1 and 2 clinical testing suggested a consistent pattern of increased anticancer efficacy, but to interpret these data, randomized trials were required to overcome the effect of stage migration and changing patterns of treatment. Historically, the disease of patients treated for castration-resistant prostate cancer was much more extensive than the disease of patients presenting for treatment in the modern era—the phenomenon of stage migration (Table 1). Therefore, the outcomes of patients with tumor progression—defined by positron emission tomography (PET) or the measurement of prostate-specific antigen (PSA) levels—treated in the modern era with newer agents may appear to be better than the outcomes of patients treated with older agents, when in fact the older agents were targeting more-extensive disease. Improved outcomes may have been incorrectly attributed solely to the effect of a new drug.¹²

In a placebo-controlled, randomized trial of 1195 patients who had previously been castrated and had received docetaxel as salvage treatment, DeBono and colleagues¹³ showed that abiraterone improved overall survival (median OS, 14.8 vs 10.9 months), time to PSA progression, progression-free survival, and PSA response rates. In a randomized trial of 1088 patients with castration-resistant disease who had not yet received chemotherapy, Ryan and colleagues¹⁴ demonstrated the superiority of abiraterone/prednisone vs placebo/prednisone. The median progression-free survival (PFS) times were 16.5 and 8.3 months, respectively, and the median OS times were not reached and 27.2 months, respectively (hazard ratio [HR], 0.75; 95% CI, 0.61-0.93; $P=.01$).

Another treatment option has been afforded by the development of MDV3100, also known as enzalutamide (Xtandi, Astellas Pharma/Medivation). This agent was designed to bind to the androgen receptor with greater affinity than that of many of the second-line agents, and it may inhibit other steps in the androgen receptor/signaling pathway. Scher and colleagues¹⁵ reported results from AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-

Table 1. Comparable Series With Migration of Age, Performance Status, and Stage in the Assessment of Mitoxantrone-Based Regimens for Castration-Resistant Prostate Cancer, Illustrating the Importance of Randomization in Assessing New Agents

Study	Tannock, ³³ 1996	Kantoff, ³⁴ 1999	Ernst, ³⁵ 2003	Berry, ³⁶ 2002	Raghavan, ³⁷ 2005
Age, y					
Median	69	72	71	70	73
Interquartile range	63-75	67-75	64-75	49-87	NA
ECOG PS, %					
0	6	}85	13	75	4
1	57		62	23	79
≥2	37		25	2	18
Metastases, %					
Bone	98	91	NS	86	93
Lung	}4	21		2	10
Liver		9		4	17
Nodes	22	9		18	28
PSA, ng/mL					
Median	209	150	150	57	210
Interquartile range	66-678	52-362	45-361	4-2375 ^a	77-430
Alkaline phosphatase					
Median	2.0 (SI U)	167	229	NS	355
Range	1.0-5.3	105-317	150-495		44-3018
With pain, %	99	Not defined	100	0	100
On narcotic analgesics, %	Not defined	Not defined	22	0	100
2-y actuarial survival, %	~15	~20	~15-17	~15	21 ^b

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available; NS, not stated; PSA, prostate-specific antigen; SI U, Système International d'Unités units; y, years.

^aTotal (not interquartile) range.

^bActual, not actuarial, survival of patients treated with mitoxantrone plus tesmilifene, a biochemical modulator.

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based Chemotherapy), which compared enzalutamide vs placebo after the failure of castration and salvage chemotherapy. The median OS times were 18.4 and 13.6 months, respectively, with major improvements in all secondary endpoints noted in the patients who received enzalutamide.

Loriot and colleagues¹⁶ reported, in a prespecified subset analysis of this trial, that 12-month OS, radiographic PFS, and PSA response rates were all improved in patients with visceral metastases (liver or lung). This is an important observation in view of the relative resistance to treatment of visceral metastases in prostate cancer unless they are associated with neuroendocrine differentiation.

A direct comparison with bicalutamide, a standard second-line nonsteroidal antiandrogen (with less affinity for the androgen receptor) in widespread use against relapsed metastatic prostate cancer, was recently completed.¹⁷ In STRIVE (Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men With Prostate

Cancer), a mixed population of patients with metastatic (n=257) or nonmetastatic (n=139) disease was randomly assigned to 160 mg of enzalutamide per day or 50 mg of bicalutamide per day. PFS was the primary endpoint because of the high likelihood that multiple subsequent treatments would contaminate OS as the primary endpoint. The median PFS times were 19.4 and 5.7 months, respectively, with all secondary endpoints favoring enzalutamide, although it is disappointing that OS data were not reported.

In PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer), a randomized trial that compared enzalutamide with prednisone, Beer and colleagues¹⁸ treated 1717 patients who had castration-resistant prostate cancer. The trial was stopped at a planned interim analysis after 540 deaths when it was revealed that the rate of radiographic PFS at 12 months was 65% in the experimental arm vs 14% in the placebo

arm, accompanied by a 29% reduction in the risk for death. All secondary endpoints showed similar benefit from enzalutamide treatment, but both arms had median OS times of less than 3 years.

Although beyond the scope of this review of the first-line use of novel hormonal agents, it is worth noting that cytotoxic agents such as docetaxel, mitoxantrone, and cyclophosphamide produce OS and various secondary endpoints in castration-resistant prostate cancer that are well documented and similar to those achieved with abiraterone and enzalutamide as second-line hormonal therapy.¹⁹⁻²¹ As noted earlier, the older studies treated mostly patients with higher-volume disease, and thus direct comparisons are difficult. Although historical comparisons have well-known limitations,¹² true comparison will be available when the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial) series of trials mature and are published in the peer-reviewed literature. Nonetheless, this preliminary comparison supports continued exploration of the roles of novel hormonal therapies, especially because the reported toxicity profiles generally indicate that toxicity is less severe than with chemotherapy.

The Emerging Understanding of Androgen Receptor Function

Recent data have shown that in the chronically androgen-deprived environment, the ligand-binding end of the androgen receptor may be lost in the presence of androgen receptor splice variant 7 (AR-V7), an abnormally spliced messenger RNA (mRNA) isoform of the androgen receptor. As a result, the androgen receptor cannot be affected by the second-generation hormonal agents abiraterone and enzalutamide. Nonetheless, it remains constitutively active as a transcription factor.²² Thus, although it is unable to bind ligands such as dihydrotestosterone, it is capable of driving growth in castration-resistant prostate cancer.²³ In a small pilot study, lower PSA response rates and shorter PFS times in response to treatment with abiraterone or enzalutamide were documented in association with expression of AR-V7 in circulating tumor cells.²² In a more detailed study, Antonarakis and colleagues²³ confirmed their preliminary data in a series of more than 200 patients and demonstrated that the presence of circulating tumor cells expressing AR-V7 was associated with the worst outcome. The absence of any circulating tumor cells was associated with the best PSA response, duration of remission, and OS; results were intermediate for patients with AR-V7-negative circulating tumor cells. Patients with AR-V7-positive circulating tumor

cells had a median survival of 11.2 months (95% CI, 8.3-17.1 months) after treatment with abiraterone or enzalutamide, whereas those without circulating tumor cells had a median survival of 29.5 months (95% CI, 18.4 to upper boundary not reached). Of note, the study was not powered to assess OS at a level of statistical significance, but the data were quite compelling in view of the absolute difference in survival figures.

Similar data were reported from the Memorial Sloan Kettering Cancer Center, where a different AR-V7 assay system was used.²⁴ Researchers there showed that 18% of 161 men with advanced disease exhibited AR-V7-positive circulating tumor cells; only 3% of new patients had these circulating cells, compared with 31% of patients who had received multiple lines of treatment. A strong correlation was found between expression of AR-V7 and poor outcomes.

An important caveat that should not be forgotten is that artifacts in AR-V7 measurements can be created from the nature of blood collection. Luk and colleagues²⁵ recently reported that AR-V7 and total androgen receptor levels could be accurately measured even 48 hours after collection (with values similar to those found in early measurements) if the blood was stored in ethylenediaminetetraacetic acid (EDTA) and citrate tubes, but not if it was stored in preservative-containing tubes.

Novel Hormonal Agents for the First-Line Treatment of Prostate Cancer

Once the surprising anticancer efficacy of abiraterone and enzalutamide after the failure of initial castration (with or without an interposed therapeutic trial of salvage cytotoxic chemotherapy) had been demonstrated, it was logical to initiate trials to test the effect of these agents in initial treatment (of presumptively castration-sensitive prostate cancer).

The superiority of a regimen in which abiraterone and prednisone were added to standard androgen deprivation therapy (ADT) was recently demonstrated in 2 seminal trials. James and colleagues²⁶ reported on one component of STAMPEDE—which had a multi-arm, multi-stage platform design that made it possible to compare various novel therapies when added to standard ADT. After the authors had assessed 1917 patients with a median follow-up of 40 months, they identified treatment failures in 535 patients on standard ADT and in 248 patients on the novel combination (HR, 0.29; 95% CI, 0.25-0.34; $P < .001$). The patient population was heterogeneous, with 20% having node-positive or node-indeterminate nonmetastatic disease and 28% having no evidence of metastases to nodes or other locations. The numbers of deaths were 262 and

184 at the time of reporting, a statistically significant difference favoring the combination. The benefit was seen in the groups both the with metastatic and without metastatic disease.

However, the toxicity was substantially more severe in the novel treatment group, including a small increase in deaths related to toxicity. Grade 3 toxicity or higher was reported in 47% of the combination group and 33% of the standard arm. Increases were observed in cardiovascular disorders (10% vs 4%), particularly hypertension, as well as in hepatic dysfunction (7% vs 1%) and respiratory complications (5% vs 2%), but no significant difference was found in the iatrogenic death rate. Further monitoring for length of remission and duration of chronic toxicity will be essential.

In another randomized trial, LATITUDE (A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naïve Prostate Cancer), 1199 patients with high-risk metastatic disease were treated with abiraterone/prednisone/ADT or ADT alone.²⁷ In the first, planned interim analysis after 406 deaths, the numbers of deaths in the 2 groups were 169 (28%) and 237 (39%), respectively. The OS rates at 3 years were 66% and 49%, respectively. Secondary endpoints, including median time to progression of pain, median time to PSA progression, median time to next skeletal event, median time to chemotherapy, and median time to next prostate cancer treatment, all favored the novel combination.

The pattern of toxicity in LATITUDE was similar to that reported from STAMPEDE, with the combination and standard arms reporting grade 3 or higher toxicity in 63% and 48% of patients, respectively. The surfeit of adverse events occurred in the domains of hypertension, hypokalemia, and hepatic dysfunction. Again, longer follow-up to determine the durability of response and patterns of late side effects will be essential.

For completeness, it is noted that the MRC Clinical Trials Unit has published a meta-analysis of these 2 trials²⁸ and has included reference to an unpublished third study, PEACE1 (A Phase III of ADT + Docetaxel +/- Local RT +/- Abiraterone Acetate in Metastatic Hormone-Naïve Prostate Cancer), which addresses a similar question (but with no reported data from that study). Not surprisingly, the meta-analysis confirmed the statistically significant results of STAMPEDE and LATITUDE. Because PEACE1 provided no additional data, and the other 2 trials had already yielded consistent data with statistically significant differences favoring abiraterone/prednisone/ADT, it is unclear why publication of this meta-analysis was viewed as necessary.

It should not be forgotten that other advances in the first-line treatment of metastatic prostate cancer have

been reported in the last few years. Sweeney and colleagues,²⁹ reporting the comparison of initial docetaxel/ADT vs ADT alone, showed the important effect of the chemohormonal combination for patients with newly diagnosed, poor-risk metastatic prostate cancer. A smaller effect was seen in patients with less-extensive metastatic disease. These data were confirmed by another arm of the STAMPEDE trial.³⁰ Given the increasing focus on cost and toxicity, the determination of an optimal approach to the management of newly diagnosed metastatic prostate cancer will become increasingly important, and it may even be that differences in the effects of chemohormonal treatment vs abiraterone- or enzalutamide-based regimens may become apparent depending on the stage of disease and initial expression of AR-V7.

Conclusion and Thoughts for the Future

It is thus clear that the possibility of a new standard in the treatment of newly presenting metastatic prostate cancer exists in view of the substantially improved outcomes in 2 randomized trials. A longer period of follow-up, perhaps augmented by the publication of the results of PEACE1, will strengthen the position of abiraterone within the frontline armamentarium. Similarly, evidence will become available regarding the potential similar use of enzalutamide. Important considerations will include long-term survival, patterns of toxicity, and cost.

One important issue, summarized in Table 2, is the substantial difference between the survival figures of the Southwest Oncology Group (SWOG) trial of continuous vs intermittent initial hormone therapy⁸ and those of the control arms of the STAMPEDE and LATITUDE studies. The difference is most likely caused by the fact that the SWOG study required a PSA response before randomization, creating a case selection bias when only OS was considered. This is another example of the fallacy of relying upon historical comparison and the importance of randomized clinical trials. That said, the data from STAMPEDE and LATITUDE are relatively early reflections of the effect of adding abiraterone to ADT for previously untreated prostate cancer, and careful long-term follow-up and reporting will be required.

Other important questions remain that may be answered by STAMPEDE and other extant studies:

- Should ADT be used initially with docetaxel or with abiraterone or other novel hormonal therapies?
- Does the initial risk attribution (eg, poor-risk metastatic disease) influence this decision?
- Is the increased pattern of toxicity with ADT plus cytotoxics, compared with the abiraterone combination, justified by the difference in outcomes?

Table 2. Comparable Series With Stage Migration for the Initial Treatment of Newly Presenting Metastatic Prostate Cancer

Study	Hussain, ⁸ 2013	Sweeney, ²⁹ 2015	James, ²⁶ 2017	Fizazi, ²⁷ 2017
Comparators	INT vs CONT	ADT vs ChemoADT	ADT vs ABI/ADT	ADT vs ABI/ADT
Age, y				
Median	70 vs 70	63 vs 64	67 vs 67	67 vs 68
Interquartile range	39-97 vs 39-92	39-91 vs 36-88	62-72 vs 63-72	33-92 vs 38-89
ECOG PS, %				
0	96 vs 96	69.2 vs 69.8	78 vs 78	NA
1	4 vs 4	29.3 vs 28.7	} 22 vs 22	
≥2		1.5 vs 1.5		
Metastases, %				
Extensive	49 vs 47	63.6 vs 66.2	NA	14 vs 14
Minimal	51 vs 53	36.4 vs 33.8		NA
Visceral	7.1 vs 6.3	16.8 vs 14.4		2 vs 3
PSA, ng/mL				
Median	41 vs 43	52.1 vs 50.9	56 vs 51	NA
Interquartile range	15-132 vs 15-142	0.1-8056 vs 0.2-8540	19-165 vs 19-158	
Median survival (metastatic cancer), mo	61 vs 67	44 vs 57	48 vs NR	36 vs NR

ABI, abiraterone; ADT, androgen deprivation therapy; ChemoADT, chemotherapy/androgen deprivation therapy; CONT, control group; ECOG PS, Eastern Cooperative Oncology Group performance status; INT, intervention group; mo, months; NA, not available; NR, not reached; PSA, prostate-specific antigen; y, years.

- Do the differences in outcome justify the differences in cost?
- Are there relevant differences in patterns of late toxicity or duration of remission or survival patterns?
- How will molecular prediction and prognostication influence the decision process?

It is highly unlikely that historical comparisons will resolve these questions for reasons discussed in detail elsewhere,¹² and we will therefore have to depend on the completion of current randomized clinical trials, as well as the design and completion of studies that address the issues that will remain unresolved. Many of the less-experienced current “opinion leaders” frequently opine that new agents have completely replaced some of the old standards, such as the taxanes, mitoxantrone, doxorubicin, and the alkylating agents. We should remember that this opinion remains unproven and supports the routine use of expensive novel compounds over cheaper active agents. In the present era, such an uninformed and unproven stance simply cannot be accepted. Table 1, which is designed to show the effect of stage migration and the need for randomized trials in assessing new agents, additionally reminds us of the utility of one of the older standards, particularly in the context that patients in that era were usually treated when they

had more advanced, bulky disease. Also worth noting is a recent nonrandomized, retrospective, “real-world” study (with all the attendant limitations) that compared abiraterone/enzalutamide vs taxane treatment for castration-resistant prostate cancer within the Veterans Health Administration hospitals.³¹ Although possibly influenced by case selection biases that were not identified, this study did not show any significant difference between outcomes of the 2 classes of treatment, further mandating the need for more data before standards of care are changed.

With regard to molecular prognostication and prediction, it is already clear that expression of AR-V7 correlates with the outcomes of treatment by the novel androgen receptor–targeting agents. In addition, a recent study has suggested that circulating tumor DNA representing defects in *BRCA2* and *ATM* is associated with poor outcomes.³² The study also confirmed that somatic alterations in *TP53* are independently associated with the rapid development of resistance to androgen receptor–targeting agents. These studies are a harbinger of much more extensive, multigene, whole-exome, and deeply targeted sequencing studies that may help to shape treatment strategies.

Clinicians experienced in the treatment of advanced prostate cancer are well aware that early results with novel approaches often do not translate into long-term gain,

and that there is often a disconnect between the initial data presented in abstract form and at meetings and the outcomes reported in the peer-reviewed literature. For this reason, I have not attempted to speculate about data that have not yet been peer-reviewed. What is important is that this era has shown potentially important improvements in outcome based on careful translational research that has been extended into clinical practice through the completion of well-constructed early-phase studies, with data confirmed in randomized cancer trials.

Disclosures

Dr Raghavan has no disclosures to report.

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