Androgen deprivation therapy for advanced prostate cancer: why does it fail and can its effects be prolonged?

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Androgen deprivation therapy (ADT) has been the cornerstone of treatment for advanced prostate cancer for over 65 years. Although there can be worrisome side effects, data will be presented that for men with metastatic prostate cancer, immediate ADT can reduce the likelihood of developing the rare but catastrophic sequellae of metastatic disease, although it is unlikely to prolong survival compared with waiting for symptoms before initiating ADT. Additionally, for patients with extremely high risk prostate cancer that is not distantly metastatic (e.g. have a life expectancy from prostate cancer less than 10 years with all other available treatments except immediate ADT) and, whose life expectancy from non-prostate cancer diseases is excellent during this period, early ADT both alone and in conjunction with definitive local treatment prolongs survival. Moreover, ADT seems to be most effective when the cancer volume is low. However, eventually most men receiving ADT experience disease progression.

The biological mechanisms explaining how prostate cancer escapes from ADT's control include:

1) Alterations in the androgen receptor (AR) and in the AR co-factors (which modify the responsiveness of the AR to androgens) allow molecules and medications which are not normally AR agonists to act as agonists.

2) The human prostate gland, and particularly prostate cancer, may be able to synthesize androgens from both cholesterol and adrenal androgens. This may occur because prostate cancer tissue has higher concentrations of androgens than does the serum in patients receiving ADT. Thus, castrated men may not be starving their prostate cancers of androgens.

3) The AR in prostatic stroma far more strongly stimulates both malignant and benign prostatic epithelial growth than the epithelial AR does. Indeed, the epithelial AR, particularly in advanced prostate cancer, may have anti-proliferative and anti-tumor progression properties. That is, the AR in the prostatic epithelial cells, particularly malignant ones, may act as a tumor suppressor. Thus, by inhibiting the epithelial AR, its protective effects may be abrogated.

The controversial nature of these concepts, as well as the clinical and experimental data which support and question them, will be presented. Additionally, strategies for addressing each of these escape mechanisms, which may be able to prolong responsiveness to ADT, will be discussed.

Key Words: androgen deprivation, prostate cancer, androgen receptor, androgen independent, hormone therapy

Introduction

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy in the United States with 186,320 new cases and 28,660 deaths expected in 2008, making this the second leading cause of cancer-related mortality for American men.[1] Nearly all of the men who die from advanced prostate cancer will experience disease progression while receiving androgen deprivation therapy (ADT). Although ADT has been the cornerstone of treating advanced and metastatic prostate cancer for more than 65 years,[2] the optimal patient population, form of therapy, and timing of treatment are still being actively investigated and defined.

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Methods of ADT

ADT can be achieved via surgical or medical means, Table 1. Orchiectomy is one of simplest, fastest, and cost effective methods of achieving the castrate state.[3] Body image concerns, as well as its irreversibility, have made this option less appealing than medical approaches.[4] Medical castration can be administered orally (estrogens, steroidal or nonsteroidal antiandrogens) or via injections (luteinizing hormone receptor hormone

TABLE 1. **Methods of androgen deprivation**

	Method	Route of administration	Advantages	Limitations	Effect on serum testosterone (T) and estrogen (E)
Surgical castration					
	Orchiectomy	Trans-scrotal surgery	Fast time to castrate levels of T Inexpensive Little morbidity, outpatient procedure	Psychological impact Irreversible Does not address adrenal androgens	↓T ↓E
Medical castration					
	Estrogens	Oral	Inexpensive Effectively reduce serum T Prevents loss of bone mineral density	Significant risk of thromboembolic event Gynecomastia Not considered first line treatment	↓T ↑E
	LHRH agonists	Injection	Effective without cardiovascular risk of DES Reversible	Requires repeated dosing Induces "surge" and "flare" phenomena	↓T ↓E
	LHRH antagonists	Injection	No "surge" or "flare"	Risk of anaphylaxis Withdrawn by manufacturer	↓T ↓E
	Nonsteriodal antiandrogens	Oral	Can prevent tumor "flare" when given with LHRH agonists Preserves libido/ potency in some men Can be used as monotherapy or in addition to other agents for combined androgen blockade	Dosing varies from daily 3 times/day dependingon formulation Preserves libido/potency Potential lethal side effects (uncertain mechanism) Cost	↑T ↑E
	Steroidal antiandrogens	Oral	Widely used in Canada and Europe	Not recommended for use as monotherapy due to increased cardiovascular risks Not available in United States	↓T ↑E

The side-effects associated with each method of ADT are due to (and can be predicted by) their impact on serum T and E. Reproduced with permission from Expert Opinion on Pharmacotherapy. E. A. Singer, D. J. Golijanin, H. Miyamoto, E. M. Messing. Androgen deprivation therapy for prostate cancer. 2008;9(2):211-228.[60]

TABLE 2. **Androgen deprivation regimens**

Method	Indications	Advantages	Limitations
Combined androgen blockade	Locally advanced and metastatic disease	Small survival advantage over LHRH or surgical castration alone	Increased frequency of side effects, added cost
Sequential androgen blockade	Uncertain	May improve sexual function in some men	Investigational
Triple androgen blockade	Uncertain	Most complete androgen deprivation May target stromal AR	Investigational
Antiandrogen monotherapy	Locally advanced	More favorable side effect profile over castrative therapies	Not indicated for localized disease
Antiandrogen withdrawal syndrome	Increasing PSA while on NSAA	Can cause a temporary decrease in PSA	Response usually only lasts weeks to months
Intermittent androgen deprivation	Locally advanced and metastatic disease	May prolong time to progression in the face of ADT Improved quality of life during off periods Decreased cost of treatment	Investigational

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[LHRH] agonists or antagonists); depot formulations permit patients to receive treatment only several times per year.[5] Medical castration may also be stopped, allowing for intermittent ADT. Medical or surgical castration may be combined with antiandrogens in order to block adrenal androgens (combined androgen blockade), or with agents that block the conversion of testosterone to dihydrotestosterone (sequential androgen blockade), or with both of these classes of agents (triple androgen blockade), Table 2.

Timing of ADT

"When to initiate ADT?" is one of the most challenging questions facing all physicians who treat prostate cancer. Traditionally, ADT was reserved for men with symptomatic advanced or metastatic prostate cancer.[6,7] Published in 1997, the MRC study indicated that earlier initiation of ADT, particularly for men without metastases, could prolong survival in patients who had advanced local regional disease.[8,9] Subsequently, ADT as a primary treatment for localized disease became increasingly popular.[10,11] However, mounting evidence has shown that primary ADT (PADT) is not usually beneficial for men with cancer confined to the prostate.[12-14] Lu-Yao and colleagues recently reported that in their population based cohort study of more than 19,000 men over 66 years of age (median 77 years) with clinically localized prostate cancer, PADT was not associated with a cancer specific survival advantage compared to watchful waiting but did expose all the subjects to the side effects and financial costs associated with androgen deprivation.[15] The likely reason for this is that most of these patients had a limited life expectancy and localized prostate cancer rarely grows rapidly enough to be lethal over a 5 to 10 year time horizon, well longer than the overall life expectancy of these men. It is for these reasons that the American Urological Association did not include PADT among its recommended therapies for clinically localized prostate cancer in 2007.[16] In a man with locally advanced prostate cancer, however, the issue is less settled and two large, prospective, randomized, phase III trials (MRC and EORTC) have reported overall survival advantages for early PADT.[8,17]

Early ADT is given in the adjuvant setting soon after definitive therapy for small volume, local regional disease. Late, or deferred, ADT is not implemented until symptomatic or radiographic metastases are present, which is essentially the classic time for initiating this therapy.

In the surgical arena, early ADT has been shown to improve overall, cancer specific, recurrence free, and biochemical recurrence free survivals in men with node positive disease after radical retropubic prostatectomy/pelvic lymphadenectomy (EST 3886).[18,19] Men receiving early hormonal therapy also experienced fewer complications such as pain, urinary retention, and pathologic fractures.[6,8,20] When using PSA thresholds in men with biochemical recurrence after radical retropubic prostatectomy as a trigger for initiating ADT, early treatment improved progression free survival and prostate cancer specific survival compared to deferred ADT.[21-23] Radiation oncologists have also seen improved overall survival by combining external beam radiation with ADT, with the greatest benefit seen in high risk patients with high Gleason grade tumors.[17,24-27]

Based on the current literature, early ADT prolongs survival in men with high risk, localized/regional prostate cancer. Two important considerations that may explain these findings are the burden of disease and life expectancy at the start of hormonal therapy. For example, the subjects in EST 3886 trial had such minimal disease after surgery that 80% of the men in each arm had undetectable PSA levels and their life expectancy was greater than 10 years in order to be surgical candidates to begin with.[18,19] It is uncertain if the same results would be seen in men with a greater amount of residual cancer or worse comorbidities. However, using early ADT in men with low and intermediate risk disease has not shown the same benefits (although there may be a role for neoadjuvant ADT plus external beam radiotherapy in intermediate risk patients[28]).

Therefore, the men most likely to benefit from early ADT are those at high risk to die from their prostate cancer within 10-12 years, but not from their competing medical comorbidities, as death due to non-cancer causes should be relatively low during this period.[19,29] Even if an appropriate candidate is treated with early ADT and receives its expected benefits, a subset will progress despite castrate levels of serum androgens. Once this occurs, median survival is only 18 months.[30] New insights into the molecular biology of the androgen receptor and prostatic homeostasis provide opportunities for new strategies to prolong the beneficial effects of ADT.

Androgens and the androgen receptor

Circulating androgens bind to the androgen receptor (AR), which has been traditionally thought to function as a ligand inducible transcription factor, resulting in prostatic cellular growth.[31,32] In addition to androgens, other sex steroids (estrogens, progestin) and adrenal steroids (glucocorticoids, mineralocorticoids), reninoids, vitamin D, thyroid hormones, and fatty acids have the potential ability to activate the AR, but rarely do so.[32-35] Coregulator molecules modulate AR transcription events by affecting ligand selectivity and DNA binding capacity.[36-39] Despite ADT's initial efficacy in treating nearly all men with prostate cancer, when patients develop androgen independent or hormone refractory disease, which is hallmarked by rising serum PSA levels and tumor growth despite medical or surgical castration, alterations in the AR are often thought to be at work.[40] It is important to note that "androgen independence" does not necessarily mean independence from the AR. The exact mechanism that allows prostate cancer to escape the control of hormonal therapy is unclear, but several models offer intriguing potential explanations.

Transformation into androgen independent disease

One hypothesis is that the AR becomes "superactive," meaning that tumor cells possess more androgen binding sites than their androgen sensitive cohorts and that the AR may be transcriptionally active despite a paucity of testosterone and dihydrotestosterone.[41-44] Additionally, since prostate tumor cells have higher levels of androgens than those in the serum or surrounding benign tissue, the laboratory definition of "castrate" may not be clinically adequate. Evidence also exists indicating that recurrent prostate cancer, in the presence of ADT, can synthesize androgens from cholesterol or adrenal androgen precursors.[45] Agents that block androgen synthesis, such as abiraterone, may play an increasingly important role in the treatment of androgen independent prostate cancer.

A second mechanism involves the liberation of AR activation from rigorously restricted ligand binding. Molecules other than androgens, including cytokines, interleukins, and protein kinases, have been shown to activate the AR, allowing protein translation and cellular proliferation in the absence of traditional ligands.[46-48] These growth factors have been found in increased concentrations in the primary prostate tumor and metastatic sites of men with androgen independent disease,[49-51] strengthening their potential

link as a nonandrogen stimulus for tumor progression via the acetylation or phosphorylation of the AR.[52,53]

Third, as seen in some patients treated with combined androgen blockade, antiandrogens may paradoxically stimulate tumor growth while antiandrogen withdrawal will bring about a temporary decrease in disease burden and PSA. Point mutations in the AR have been identified that allow it to recognize antiandrogens as agonists.[54,55] Additionally, alterations in AR coregulator function can facilitate the AR's use of antiandrogens and nonandrogenic steroid hormones as agonists.[56-58]

A new view of the androgen receptor

The role of the AR, as a promoter of both benign and malignant cellular growth, is more complex than initially believed. In an elegant series of experiments, Niu and colleagues have found that the AR acts as both a tumor suppressor and proliferator in prostate cancer.[59] By creating a mouse prostate cancer model that lacks the AR in its prostatic epithelium only, gain and loss of function studies were able to be performed in epithelial stromal cell cultures and with coimplantation experiments in order to determine the impact of the AR on prostate cancer progression and invasion. In the prostatic epithelium the AR can function as a tumor suppressor preventing invasion and metastases, while in the stroma it can function as a promoter of cancer invasion and progression. The loss of epithelial AR expression, therefore, may be a poor prognostic indicator (and unintended consequence of conventional ADT which lowers androgen levels throughout the body, suppressing AR activity in both the epithelium and stroma) as tumor cell invasion was seen in both *in vitro* and in *vivo studies*. Such dual functioning of the AR is not unique to the prostate, as the AR in the skin of the scalp induces hair loss while the AR in the skin of the face induces hair growth.

Conclusions and new directions

ADT will continue to be a vital weapon in the urologic oncologist's armamentarium against prostate cancer. However, all current hormonal treatments focus on ligand binding and not on the function of the AR itself. As elucidated by Niu and colleagues, the AR is a more complex entity than previously recognized. New treatments for prostate cancer, both hormone sensitive and androgen independent, will need to selectively target the AR itself in specific tissues (targeting the prostatic stromal AR while sparing the epithelial AR). Prostate cancer specialists of all disciplines will need to renew their commitment to prospective, multicenter, collaborative trials in order to realize the potential benefits of new androgen/AR targeted approaches for men with advanced prostate cancer.

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