Traditional androgen ablation approaches to advanced prostate cancer: new insights

Kyle O. Rove, MD, E. David Crawford, MD
Division of Urology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

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Introduction: *Androgen deprivation therapy (ADT) is a mature therapy for the treatment of advanced prostate cancer, and yet despite many years of use, there is still much about its use, side effects, efficacy, and outcomes for which the urology community does not have answers.*
Materials and methods: *A literature search was performed to review ADT use in the modern era, specifically examining adjuvant ADT after primary therapy, continuous versus intermittent ADT, disadvantages of luteinizing hormone releasing hormone (LHRH) agonists versus newer LHRH antagonists, and controversies of combined androgen blockade.*
Results: *ADT has little role as primary therapy in North American populations. Evidence for the use of neoadjuvant/adjuvant ADT with radical prostatectomy is less compelling than that for radiation therapy. Data supporting combined androgen blockade over LHRH agonist therapy alone are mixed. Newer LHRH antagonists have a faster onset of reduction in serum testosterone and demonstrate other effects on serum follicle stimulating hormone (FSH) that may impact prostate cancer outcomes.*
Conclusions: *ADT remains a mainstay of treatment in prostate cancer, and our knowledge of its effectiveness has improved with time. There are still scenarios where not enough information is available and study is ongoing.*

Key Words: androgen deprivation therapy, prostate cancer, castration resistant prostate cancer, androgen receptor, CRPC

Introduction

Advanced prostate cancer arises in several forms, either recognized because of rising prostate-specific antigen (PSA) after failing primary treatment or, more ominously, bone pain or urinary symptoms signifying locally advanced disease or metastasis. Fortunately, the latter is rare in the modern era. All of these entities, however, are driven by ongoing stimulation and downstream signaling from the androgen receptor (AR). By eliminating ligand (namely serum testosterone), this activity can be markedly downregulated as first discovered by the work of Huggins and Hodges, who were ultimately awarded the Nobel Prize in 1966.[1] Since that time, bilateral orchiectomy has been replaced with medical alternatives, including luteinizing hormone releasing hormone (LHRH) agonists, antagonists, and combined androgen blockade (CAB). The effect of these regimens, however, is limited, as nearly all patients with advanced disease will, if maintained on androgen deprivation therapy (ADT), develop resistance requiring alternative therapies. This review examines traditional strategies to the use of androgen ablation in patients with advanced prostate cancer.

Address correspondence to Dr. E. David Crawford, Section of Urologic Oncology, Mail Stop #F710, P.O. Box 6510, Aurora, CO 80045 USA

LHRH analogues

The decapeptide LHRH was first discovered in 1971 by Dr. Schally, who further demonstrated that synthetic analogues would bind to their receptors in the anterior pituitary to result in agonist activity.[2] Physiologic activity occurs via LHRH release from the hypothalamus in a pulsatile manner.[3] It then acts on the anterior pituitary to induce the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn act on the testes. Ninety to ninety-five percent of circulating androgens are produced by the testes, with the remainder coming from the adrenal glands.[4] With prolonged exposure to LHRH, the anterior pituitary downregulates LH and FSH, which in turn leads to lower testosterone, thus forming the basis for modern medical ADT in the treatment of prostate cancer.[5]

Up to this time, however, bilateral orchiectomy constituted the gold standard of hormone therapy for prostate cancer, but estrogenic compounds were also being used to lower testosterone (e.g., diethylstilbesterol, DES). Once LHRH analogues were deemed safer than estrogens (fewer thromboembolic side effects and cardiovascular events) and palliated advanced prostate cancer patients well, LHRH agonist therapy supplanted estrogens and bilateral orchiectomy.[6] Bilateral orchiectomy remains an option, and the side effect profile is similar to LHRH therapies (vasomotor symptoms, weight gain, mood lability, gynecomastia, fatigue, cognitive changes, and loss of libido). While bilateral orchiectomy is very efficacious and more cost effective at rapidly lowering total testosterone ($t_{½}$ 45 minutes, mean serum testosterone nadir 14 ng/dL seen in about 8.6 hours ± 3.2 hours), is not frequently performed in the modern era for a few reasons: the procedure is irreversible, and men are thought to experience significant psychological impact.[7-10] When given the choice of medication versus bilateral orchiectomy, one study noted 78% would choose medication to avoid surgery and out of convenience.[11] The reversible nature of LHRH analogues was further enhanced with the introduction of depot formulations, which last anywhere from 1-12 months before requiring re-dosing. A meta-analysis of 27 randomized controlled trials demonstrated similar efficacy between surgical and medical modalities of ADT.[12]

ADT is now standard of care in advanced prostate cancer, but it has been studied in other settings such as monotherapy for localized disease, early stage disease, neoadjuvant and adjuvant therapy in combination with surgery or radiation therapy. The practicing physician will undoubtedly encounter patients with various disease states and preferences. Below, we endeavor to summarize and review pertinent questions related to the modern accepted uses for ADT.

ADT as primary therapy

Some men may wish to avoid the side effects of definitive local therapy (radical prostatectomy or radiation therapy). Active surveillance is a valid option, particularly in men with low risk disease. The use of ADT for primary treatment is discouraged on the basis of randomized controlled trials comparing ADT alone to ADT plus radiation.[13] In one study by Widmark et al, 875 patients with either localized or locally advanced prostate cancer received either 3 months of LHRH agonist therapy plus non-steroidal antiandrogen or the same plus radiotherapy (minimum 70 Gy). After 10 years, overall mortality favored the ADT plus radiation arm (29.6% versus 39.4%).[14] The reader will note that modern ADT regimens are given for longer durations. The CAN-NCI-C-PR3 study examined men with high risk localized disease (T2 N0, PSA > 40 ng/mL or PSA > 20 ng/mL and Gleason ≥ 8) or locally advanced disease (T3/T4 N0) and randomized them to either lifelong ADT or ADT plus external beam radiation therapy. Men treated with ADT and radiation therapy had significantly lower overall risk of death (hazard ratio 0.70, 95% CI 0.57-0.85, p = 0.001).[15] Comparisons of ADT alone to ADT plus radical prostatectomy show similar poor outcomes for ADT monotherapy but are retrospective in nature.[16-18]

Despite current recommendations in the United States (U.S.) and Europe against the use of ADT as monotherapy for prostate cancer, 14.4% of patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry received only ADT as a form of therapy for prostate cancer in an analysis of the changing treatment patterns for prostate cancer between 1990 and 2007.[19] Interestingly enough, guidelines in Asia endorse monotherapy for localized prostate cancer on the basis that men have much better outcomes. One recent comparison of primary ADT patients between US and Japanese cohorts demonstrated a hazard ratio amongst all-cause mortality of 0.27 (95% CI 0.24-0.30) favoring Japanese patients.[20] The underlying reasons for these disparate outcomes is not entirely clear, but is likely multifactorial including genetics, environmental and/or dietary factors and comorbidities.

Neoadjuvant and adjuvant ADT

Investigators hypothesized that giving patients ADT prior to surgery might improve various clinical

and pathologic outcomes. A recent meta-analysis examined 10 studies comparing radical prostatectomy alone to neoadjuvant ADT followed by radical prostatectomy.[21] Overall, patients generally had T1-T3 disease with and without evidence of lymph node involvement, although the majority of patients across the studies were T1 and T2. Three of ten studies used an LHRH agonist alone, and seven studies used CAB. Overall survival was not significantly different between the two groups. Studies did demonstrate reduced positive margin rates ($p < 0.00001$), improved rates of organ confinement ($p < 0.0001$) and decreased lymph-node invasion ($p < 0.02$) when compared to radical prostatectomy alone. Longer durations (6 or 8 months) of neoadjuvant ADT versus shorter ones (3 months) improved pathologic outcomes. Currently, neoadjuvant ADT is not recommended prior to surgery.

In the adjuvant setting after radical prostatectomy, Messing et al looked at 98 men with positive pelvic lymph nodes found at time of surgery. These patients were randomized to either immediate ADT or observation. After a median follow up 11.9 years, improvements in overall survival, cancer-specific survival and progression-free survival were noted in patients who received immediate lifelong ADT.[22] Conversely, Iversen et al noted that in men with localized disease, adjuvant ADT (bicalutamide 150 mg daily) after primary therapy demonstrated no additional benefit over those who received primary therapy alone.[23] SWOG S9921 randomized 983 men with high risk features at prostatectomy (any of the following: Gleason ≥ 8, preoperative PSA > 15 ng/mL, stage T3b or greater, N1 disease, positive margin, or Gleason 7 plus PSA > 10 ng/mL) to either adjuvant ADT (goserelin plus bicalutamide) or adjuvant ADT plus mitoxantrone chemotherapy. Final treatment comparisons are not due to be reported until 2017.[24] For now, standard of care remains adjuvant RT in patients with these high risk features after radical prostatectomy. Based on the Messing data, however, adjuvant ADT does show benefit in patients with positive lymph nodes at time of surgery.[22]

With regards to patients receiving primary radiation therapy, there are a multitude of studies examining patient selection (low versus intermediate versus high risk disease), duration of therapy (6 months versus 3 years), timing of therapy (neoadjuvant versus adjuvant). Bolla et al first demonstrated benefit to adjuvant ADT for 3 years in men undergoing primary radiation therapy.[25] The most recent follow up data shows a striking difference in overall survival between those who received radiation alone (39.8%) versus radiation plus ADT (58.1%). The majority of patients had T3 disease, and the combination therapy arm overall survival hazard ratio was 0.60 (95% CI 0.45-0.80, $p = 0.0004$).[26] Other important studies have clarified other important points: adjuvant ADT does not benefit patients with low risk, localized disease;[27] intermediate risk localized prostate cancer patients do well with shorter duration of ADT (4-6 months);[28] and, high risk patients benefit from longer treatment (3 years).[29] Another study showed no difference between progression-free survival in patients undergoing radiotherapy who received neoadjuvant versus adjuvant ADT.[30]

Continuous versus intermittent ADT

Another strategy of ADT administration comes in the form of "drug holidays" wherein patients allow serum testosterone or PSA levels to recover and then repeat administration. The basis for such treatment evolved from the idea that if the time hormone-sensitive prostate cancer spent in an androgen-deficient state were drawn out, the time to castration resistant disease could be prolonged, improving patient outcomes.[31] In vitro models further showed that hormone-sensitive cells undergo repeated bouts of apoptosis in response to cyclic androgen deprivation.[32] Mouse models further demonstrated that this cyclic activity prolonged the time to a castration resistant disease state.[33,34] Other hypothesized benefits include improved quality-of-life, improved costs, and fewer adverse events associated with ADT.

A phase III trial was conducted that randomized men who had previously undergone primary therapy (radical prostatectomy or radiotherapy) to either continuous ADT (LHRH agonist with concomitant non-steroidal antiandrogen) or intermittent ADT (8 month treatment cycles, non-treatment cycle began after 8 months if there was no evidence of disease progression and PSA was < 4 ng/mL). On-therapy cycle resumed when the PSA rose to 10 ng/mL. The primary endpoint was overall survival. A total of 1,386 patients were randomized. The hazard ratio for death in the intermittent arm was 1.03 (95% CI 0.86-1.23), indicating no significant advantage. With regards to non-inferiority of the intermittent strategy, the p value was 0.01.[35] Although non-inferior, many questions with regards to intermittent ADT remain unanswered with respect to treatment schedules (PSA-based, calendar-based, or testosterone-based) and quality-of-life outcomes.

A second trial by Hussain et al recently reported results in 2013, randomizing men with newly diagnosed, metastatic, hormone-sensitive prostate

cancer to either continuous or intermittent therapy.[36] Intermittent dosing schedule was similar except the PSA-based schedule was set at 20 ng/mL before restarting ADT (or above 10 ng/mL at the investigator's discretion). Total time spent on protocol was 19 and 17 months for the intermittent and continuous arms, respectively. Patients receiving intermittent therapy spent 47% of time on ADT. Median overall survival was 5.7 years (intermittent) versus 6.4 years (continuous) after enrollment, with a hazard ratio for death in the intermittent arm of 1.10 (90% CI 0.99-1.23). With respect to non-inferiority, the study could not rule out a 20% chance of greater risk of death with intermittent therapy. This study did demonstrate intermittent therapy patients experienced better erectile function and mental health ($p < 0.001$ and $p = 0.003$, respectively) at month 3 but not at later time points.

More such trials to answer questions of different schedules are needed to fully elucidate the meaning of these two large randomized controlled trials. In fact, one study that examined different dosing scheduled noted testosterone-based dosing carried a significantly lower risk of PSA progression (hazard ratio 0.65; $p < 0.02$) as compared to continuous dosing.[37]

Disadvantages of LHRH agonists

Although LHRH agonists have been extremely successful in treating various prostate cancer disease states, they do possess some disadvantages and side effects. With regards to disadvantages, LHRH agonists will initially cause stimulation of the anterior pituitary, leading to an initial burst of LH release and subsequent testosterone flare in all patients. For about 10%, this clinical flare phenomenon can manifest itself symptomatically as acute spinal cord compression, ureteral/urethral obstruction, or bone pain. LHRH analogues take about 2-4 weeks to reach castrate levels of testosterone (defined as a serum testosterone < 50 ng/dL). Clinical manifestation of testosterone flare can be avoided by adding a non-steroidal antiandrogen that blocks downstream AR activity during the first 4-6 weeks.[40] The antiandrogen does not block the initial flare in testosterone, but rather blocks signaling activity via AR. Beyond the initial flare phenomenon, there is evidence to suggest that microsurges occur with repeat administrations of LHRH agonists in a small proportion (around 6%) of patients.[41]

Furthermore, not all patients treated with LHRH agonists will achieve a castrate level of serum testosterone of < 50 ng/dL (3.5%-17%).[41-44] The definition of castrate levels of serum testosterone remains hotly debated. The current definition of 50 ng/dL is based on the lower limit of detection for a double-dilution isotope technique to determine testosterone levels that is no longer performed.[45] Current liquid chromatography/tandem mass spectrometry (LC/MS-MS) assays have a much lower limit of detection and demonstrate that the mean serum testosterone level achieved with either surgical or medical ADT approaches 15 ng/dL.[42] As such, experts have argued that the cut off be moved to 20 ng/dL.[8] If this definition were used, up to 13%-37% of patients on LHRH agonist therapy might not have truly castrate levels of serum testosterone.[46-48]

There are suggestions from some series that inability to achieve or maintain castrate levels of testosterone confer patients worse outcomes in terms of overall survival. Morote et al examined men with non-metastatic prostate cancer receiving LHRH agonist. In men who experienced a breakthrough testosterone > 32 ng/dL during normal 3 month checks, mean progression-free survival was only 88 months versus 137 months in men who maintained serum testosterone levels < 32 ng/dL ($p < 0.003$).[49] Another retrospective study found those with higher levels of serum testosterone after 6 months of ADT had a 1.33-fold increase in cancer-specific mortality.[50] A large retrospective review of 2196 patients receiving radiotherapy with LHRH agonists showed no difference in biochemical-free survival between those who experienced any breakthrough > 50 ng/dL (73.1%) versus those who did not (62%, $p = 0.09$). The subgroup of men who experienced a breakthrough between 32 ng/dL and 50 ng/dL did show a significant difference in biochemical-free survival ($p = 0.048$). The authors note that patients who broke through 50 ng/dL were more likely to have an antiandrogen added to their regimen as opposed to those who experienced more mild breakthroughs between 32 ng/dL and 50 ng/dL. The authors note "these breakthroughs were less pronounced and, therefore, either unrecognized or presumed to be of lesser importance," perhaps explaining these data.[51]

LHRH agonist use has also been noted to result in increased risk of metabolic side effects such as diabetes and osteoporosis in addition to increased risk of cardiovascular events and stroke.[52-54] As such, in 2010, the U.S. Food and Drug Administration mandated that warnings be added to LHRH agonist labels.[55]

LHRH antagonists

To address some of these shortcomings, antagonists of LHRH receptors have been developed and have emerged from phase III clinical trials. This class of medications has the advantage of immediate downregulation of the anterior pituitary and would

not induce a flare phenomenon through initial agonistic activity like LHRH agonists. The first drug to be clinically approved for use, aberelix, was ultimately pulled from the market in the U.S. due to systemic allergic reactions secondary to histamine release and testosterone escapes. A next-generation compound, degarelix, was developed and tested in vitro and in vivo and does not have such histamine-releasing activity. As expected, degarelix abolishes gonadotropin and testosterone flare on initial administration and does not experience microsurges on repeat administration, while It suppresses PSA and testosterone faster than LHRH agonists ($p < 0.001$).[41] Further, because co-administration of an antiandrogen is not required to block flare, it avoids side effects from this class of medications. With respect to clinical outcomes, patients receiving degarelix experience fewer urinary tract infections (5% versus 8%). Biochemical control in patients with high risk disease (baseline PSA > 50 ng/mL) had better progression-free survival at 1 year versus agonist therapy (66% versus 54.7%, $p = 0.0245$).[56] No change in the rates of cardiovascular events, stroke, or thromoembolic events were noted before and after starting degarelix, implying an improvement over other forms of ADT.[57]

Effects on FSH

While most focus of LHRH agonist and antagonist activity has focused on the ability to downregulate or block the release of LH, many forget that physiologic LHRH also results in FSH release.[58,59] With LHRH agonists, FSH production is downregulated but recovers generally with time (mean levels declines 54.8% over baseline). LHRH antagonists, on the other hand, appear to have a more pronounced and persistent suppression of FSH (mean levels declines 88.5% over baseline).[41,60,61]

FSH, while not strictly germane to the testosterone axis that drives prostate cancer growth, has been shown to interact with receptors on prostate cancer cells and act as a stimulant for cellular growth.[62] FSH receptors are differentially expressed on prostate cancer cells and are expressed within blood vessels of various tumors.[63-66]

Combined androgen blockade

Greater suppression of androgenic activity is achieved when combining an LHRH agonist with a non-steroidal antiandrogen that blocks AR activity. There have been multiple studies examining clinical outcomes from CAB versus LHRH agonist monotherapy in various populations. Crawford et al compared two such populations (leuprolide versus leuprolide plus flutamide) in a large randomized controlled trial reported in 1989 with a median length in survival favoring CAB (16.5 months versus 13.9 months, $p = 0.039$).[67] A few years later, Eisenberger and colleagues reported a similar large randomized study, but with orchiectomy with and without flutamide showing no significant difference between the two arms.[68] A meta-analysis of trials comparing CAB (LHRH agonist plus one of the following: nilutamide, flutamide, or cyproterone acetate) to LHRH therapy alone showed a 2%-3% improvement in 5 year overall survival, but this was not statistically significant.[12] When examining just non-steroidal antiandrogens (nilutamide or flutamide plus LHRH agonist), there was a 2.9% statistically-significant advantage to CAB ($p = 0.005$). The number needed to treat with CAB is 35 to provide additional benefit in overall survival to one person.

Survival benefits offered by CAB are likely offset by increased rates of adverse events and reduced quality-of-life.[10] The conflicting results translate into guidelines. The American Society of Clinical Oncology (ASCO) recommends CAB for the initial management of metastatic, recurrent, or progressive prostate cancer, yet current National Comprehensive Cancer Network (NCCN) guidelines state that CAB provides no proven additional benefit over LHRH agonist therapy alone.[13,69] Certainly, these authors feel strongly that those patients who experience flare, microsurges or testosterone breakthroughs should undergo secondary hormonal manipulation, perhaps with the addition of an antiandrogen if one is not currently being used.

Role of testosterone levels in prostate cancer management

Measuring testosterone

One of the great difficulties in evaluating testosterone as a marker for prostate cancer remains our relative inability to accurately and precisely measure its value. As mentioned earlier, older techniques such as double-isotope dilution assay, radioimmunoassays, and chemiluminescence assays are imprecise at low levels of testosterone, such as those in children, women, and castrate men. These assays have coefficients of variability (CV) up to 40%. Large commercial laboratories have adopted more precise LC/MS-MS as the standard for measuring serum testosterone in hypogonadal men. CV still range from 2.7% to 25.6% on the same equipment and between equipment when measuring a single sample.[70] This variability

is influenced by differences in assay tolerances, lack of reference standards, and disparate sample preparation.[45] Given these problems, clinicians should be aware of the difficulty in interpreting individual values, particularly if testing is performed in more than one laboratory. This applies to data presented in this review as well, given varied testing platforms and variability that can occur at low levels of testosterone. There are initiatives underway to develop testing standards to allow equipment manufacturers to calibrate equipment.[71]

Current guidelines

Society guidelines regarding target serum testosterone levels in patients on ADT remain vague, likely owed to the lack of level I evidence. The 2013 National Comprehensive Cancer Network (NCCN) guidelines define "adequate suppression" of serum testosterone as < 50 ng/dL and is further reflected in the U.S. FDA insert provided with LHRH therapies for prostate cancer.[13] Additional hormonal manipulation is recommended for patients who do not achieve this level with current therapies. The American Urological Association (AUA) recently published guidelines on the treatment of castration resistant prostate cancer (CRPC) mentioning 50 ng/dL as the cut off for castrate levels.[72] The most recent European Association of Urology (EAU) guidelines question the need to redefine the cut off from 50 ng/dL to 20 ng/dL on the basis that a meta-analysis demonstrated similar outcomes between LHRH agonists and orchiectomy or DES at 2 years.[10,49] Arguably, better long term, prospectively collected evidence is still needed. Regular PSA and serum testosterone monitoring should occur for patients on ADT. An increase in PSA levels or the indication of clinical progression should trigger a testosterone level measurement in all cases to confirm CRPC. If testosterone is inadequately suppressed, secondary hormonal manipulation can be undertaken.[44]

Conclusions

Androgen deprivation continues to undergo refinement and is a mainstay in the treatment of advanced prostate cancer.

Disclosure

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