Intermittent Androgen Deprivation Therapy: Redefining the Standard of Care?

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As a clinical strategy, intermittent androgen deprivation therapy (IADT) has the potential to minimize adverse events associated with continuous androgen deprivation therapy while providing comparable efficacy for patients with advanced prostate cancer. Because most studies supporting IADT to date have been somewhat small and underpowered, additional large, randomized, controlled trials are needed before this strategy becomes the standard of care. However, the potential advantages of IADT, which include improved quality of life, the theoretical possibility of delaying hormone resistance, and possible reduction in expenses to the patient and health care payers, suggest it is a strategy worth further exploration.
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For men with advanced prostate cancer, continuous androgen deprivation therapy (ADT) is the mainstay of therapy, but has associated morbidity, which can include physical, metabolic, and psychologic health-related changes. Intermittent androgen deprivation therapy (IADT) has promise as a clinical strategy for minimizing these adverse events while delivering efficacy comparable to that of continuous ADT. Nonetheless, there still exists a need for documented Level 1 evidence demonstrating IADT's clinical efficacy before it can be considered more than an experimental treatment option.

State of the Data

Although ADT has become a standard treatment of metastatic and locally advanced prostate cancer, researchers have published few large, randomized, head-to-head clinical comparisons between continuous ADT and IADT. Moreover, existing studies of varying treatment strategies suggest an uncertainty and lack of uniformity regarding clinical endpoints. Nevertheless, there exists enthusiastic support for the benefits of IADT.

Continuous ADT

The rationale for continuous ADT is predicated on the assumption that both normal and malignant prostate cells require androgen stimulation via androgen receptors for growth and proliferation. Withdrawing androgens will impede malignant prostate cell growth. Thus, ADT in selected stages of prostate cancer will slow disease progression and potentially increase survival.[1-3]

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Although testosterone has not been demonstrated to directly initiate prostate cancer, it appears essential for prostate cancer cell growth. Despite the presence of many circulating androgens (eg, dihydrotestosterone [DHT], androstenedione, dehydroepiandrosterone [DHEA], and DHEA sulfate), which the body can convert to the metabolically active DHT, testosterone accounts for more than 90% of androgenic activity in the circulation.[4]

The production of testosterone, the primary circulating androgen, is controlled by the regulatory feedback between the hypothalamus-pituitary axis and the testes. Specifically, the pulsatile release of gonadotropin-releasing hormone (GnRH)—also called luteinizing hormone-releasing hormone (LHRH)—by the hypothalamus to the anterior pituitary gland occurs every 90 to 120 minutes to achieve androgen homeostasis in normal adult men. The interaction between the pituitary gland's luteinizing hormone (LH) receptors promotes release of LH into the circulatory system. This in turn induces testosterone production by binding to receptors in the testes. Working through androgen receptors on the hypothalamus and pituitary glands, testosterone exerts negative feedback on GnRH. The enzyme 5-α reductase converts testosterone within prostate cells into 5-α-DHT, which as an intracellular androgen is more potent than testosterone and has a 10-fold affinity for the androgen receptor.

Although current ADT replaces surgical castration with pharmaceutical interventions, the work of Huggins and Hodges in 1941 represented the first significant evidence supporting ADT's role in prostate cancer treatment. Their landmark publication described the concept of androgen blockade and showed that it resulted in dramatic and significant clinical remissions for metastatic disease.[5]

Conversely, varying degrees of androgen suppression therapy have resulted in dissimilar survival responses, especially for the advanced-stage patient. In the Veterans Administration Cooperative Urological Research Group (VACURG) II study, Byar and colleagues demonstrated that, for prostate cancer patients, receiving 0.2 mg of diethylstilbestrol (DES) provided insufficient androgen suppression and thus had a higher overall mortality rate in comparison with patients who received a dose of 1 or 3 mg DES, which resulted in lower castrate testosterone levels. Additionally, these trials demonstrated that men who received 0.2 mg/d of DES had significantly decreased overall survival in comparison with men taking DES 5.0 mg/d.[6]

Subsequently, drug approval studies have demonstrated evidence that supports the utility of LHRH analogues for lowering serum testosterone to levels < 50 ng/dL. For example, an open, randomized, phase III clinical trial conducted in the United Kingdom established goserelin as a medical alternative to bilateral orchiectomy.[7] Similarly, Kaisary and colleagues showed the LHRH analogue goserelin to be as effective as bilateral orchiectomy in treating metastatic prostate cancer.[8] Nonetheless, the number of patients included in this trial and the duration of follow-up were limited. Previous research has shown that LHRH agonists avoid the risk of thromboembolic events associated with estrogens such as DES.[9]

IADT

Although evidence for IADT has been reported, the trials to date have been relatively small and somewhat underpowered.[4] In fact, most of the clinical trials with IADT have been performed as single-institution phase II studies.[10] Should the evidence become more robust, then perhaps the concept of IADT may become more widely accepted.

Many factors and potential outcomes justify further research into IADT. In particular, investigators have established that intermittent chemical castration may reduce the morbidity caused by long-term hormonal therapy and may ameliorate quality-of-life (QoL) issues associated with traditional ADT; furthermore, IADT may provide the theoretical possibility of delaying

hormone resistance.[11,12] A review of 5 phase II studies demonstrated that ADT-free periods give patients improved QoL—reflected in an improved libido, sexual potency, and an enhanced sense of well-being—versus maintenance on continuous ADT.[13] Theoretical advantages of IADT may also include decreased treatment expense to the patient and the health care system, along with enhanced patient convenience, decreased physiologic toxicities of ADT, and the possible reduced onset of castrate-resistant prostate cancer (CRPC).

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Additionally, a review involving more than 1000 patients enrolled in 4 randomized, controlled, phase III trials with varying stages of disease progression concluded that, "[t]here are now compelling data to indicate that intermittent ADT should be regarded as standard therapy in prostate cancer." In the studies reviewed, IADT proved safe and at least as effective as continuous ADT. These authors concluded that IADT shortened the duration of potential toxicity of therapy, thereby improving QoL and reducing overall costs. The authors further concluded that future clinical trials should be designed to determine how to optimize and refine IADT for men with prostate cancer.[14]

A similar message comes from Calais da Silva and associates,[15] who randomized 626 patients with locally advanced or metastatic prostate cancer (of 766 who received a 3-month induction treatment) to either continuous treatment with 200 mg of cyproterone acetate daily plus an LHRH analogue, or intermittent treatment. Patients in the intermittent group ceased treatment after induction until their prostate-specific antigen (PSA) reached a predetermined level based on PSA at randomization.

Men in the intermittent cohort experienced a median time off therapy of 52 weeks. Ultimately, investigators observed that 107 patients from the continuous arm progressed, versus 127 patients from the intermittent arm. However, they observed no difference in survival between the 2 groups, whereas the intermittent group reported better sexual function and fewer side effects. Thus Calais da Silva and colleagues concluded that physicians should consider IADT for use in routine practice—after more randomized studies—because it is associated with "no reduction in survival, no clinically meaningful impairment in quality of life, better sexual activity, and considerable economic benefit to the individual and the community."[15]

European Association of Urology prostate cancer guidelines do not yet recommend IADT as a routine component of clinical practice.[16] Nevertheless, the clinical promise of intermittent hormonal therapy centers upon the premise that it might delay hormonal resistance, thereby delaying disease progression and thus ultimately prolonging life.[11,12] Yet the Calais Da Silva article "categorically demonstrates that this is not the case," according to a recent review by Patrick C. Walsh, MD[17]; instead, more study participants on IADT died of prostate cancer, but a greater number of cardiovascular deaths in men on continuous ADT balances out this discrepancy. Therefore, Walsh suggests that rather than considering IADT for routine use because it results in better sexual activity and economic benefits, "What about delaying hormonal therapy until patients have progression of disease? This achieves the same endpoints at a far lower cost."

The clinical promise of intermittent hormonal therapy centers upon the premise that it might delay hormonal resistance, thereby delaying disease progression and thus ultimately prolonging life.

In contradiction, some studies have provided support for the IADT strategy. For example, the European Organization for Research and Treatment of Cancer (EORTC) trial 30891 showed a direct relationship between baseline PSA level and the decrease to a PSA level < 2 ng/mL after 1 year of ADT.[18] This trial ultimately showed that patients with baseline PSA > 50 ng/mL and/or a PSA doubling time (PSADT) < 12 months faced a higher risk of death from prostate cancer and thus might have benefited from immediate ADT. Conversely, patients with baseline PSA < 50 ng/mL and PSADT > 12 months could have been spared the burden of immediate ADT because they were likely to die of causes unrelated to prostate cancer. Additional subset analysis of 107 of these same EORTC trial patients concluded that 75% of them reached a PSA nadir at each treatment cycle, and therefore, IADT appeared feasible and worthy of further investigation.[19]

Similarly, a meta-analysis of 1446 patients from phase II studies of varying IADT regimens concluded that the duration of biochemical remission after a period of ADT was a durable

early indicator of a patient's time to androgen-independent prostate cancer and death.[20]

Continuous ADT: Adverse Events

As already stated, the benefit of continuous ADT comes with associated adverse events, especially with increased duration of treatment. These side effects potentially include hot flashes, decreased libido, erectile dysfunction (ED), loss of bone mineral density, anemia, and mood alterations.[4] Additional side effects may also include fatigue, gynecomastia, and, for some patients, depression and cognitive dysfunction.[21] Metabolic syndrome also has been associated with ADT,[22] as have elevated risks for cardiovascular morbidity and mortality.[23]

The initial testosterone serum surge caused by LHRH agonists, which transiently increases LH release and therefore testosterone for up to 2 weeks after the initial dose, may also be deleterious for some patients. Patients most at risk for a testosterone surge include those with bladder outlet obstruction secondary to locally advanced bulky prostatic disease, those with clinically significant bone metastases whereby bone pain could be exacerbated, and patients in whom metastatic disease of the spine threatens to cause spinal cord compression.[4] Pretreating patients with a nonsteroidal antiandrogen before the LHRH agonist can partially block the clinical flare, whereas an LHRH antagonist, bilateral orchiectomy, or ketoconazole might avoid the clinical flare entirely.

Consistently Low Testosterone Levels

Although various authors set different thresholds for testosterone breakthrough (an increase in serum testosterone after a patient has achieved chemical castration (eg, T $<$ 50 ng/dL), this physiologic serum elevation seems intuitively consistent with negative clinical consequences. Presently, the optimal level of testosterone that should be achieved in prostate cancer treatment remains unknown.[4] General consensus has shifted the serum testosterone threshold for clinical castration from $\leq$ 50 ng/dL to a level of $\leq$ 20 ng/dL, approximating testosterone levels achieved by surgical castration.[24] Expert consensus meetings held in 2005 determined that serum testosterone levels $>$ 50 ng/dL during LHRH analogue therapy are clinically relevant and could impact treatment outcome.[25]

Nevertheless, no studies to date have conclusively shown the clinical benefit or survival advantage for the lower threshold. Similarly, no studies have prospectively analyzed the impact of serum testosterone levels and breakthrough increases on clinical outcome. Recently, Morote and colleagues[26] have attempted to determine optimum suppression levels and the impact of testosterone breakthrough. From their database, these investigators selected 73 patients with a histologic diagnosis of nonmetastatic prostate cancer treated with 3-month LHRH depot (continuous) who had at least 3 serum testosterone determinations in $>$ 1 year of follow-up. These investigators defined testosterone breakthrough as any serum level $>$ 20 ng/dL and defined androgen-independent progression (AIP) as 3 consecutive PSA increases postnadir.

Overall, these researchers found that testosterone breakthroughs are both frequent and linked with PSA progression, with 32 ng/dL representing possibly the lowest serum testosterone threshold that carries a clinical impact.[26] Specifically, patients for whom all 3 serum testosterone readings fell under 32 ng/dL had a mean AIP-free survival of 137 months, versus 88 months for those with any breakthrough increase above 32 ng/dL ($P < .03$).[27] "To our knowledge," the authors write, "this is the first report to establish a direct relationship between testosterone increases and AIP."

The study also included a subset of 28 patients who underwent concurrent treatment with bicalutamide to achieve maximal androgen blockade (MAB). For this subset, they noted that time to AIP was longer in patients treated with MAB than in those treated with LHRH analogues alone whether or not patients experienced testosterone breakthrough. However, this observation only reached statistical significance at a level of $\geq$ 50 ng/dL. At this level, patients undergoing MAB achieved a mean time to AIP of 115 months versus 32 months for the group without MAB ($P = .0249$). Although studies have linked MAB with adverse events and reduced QoL, the 50 ng/dL cutoff mirrors recommendations of the National Comprehensive Cancer Network.

Clinical Benefits of Low Testosterone

For patients with clinically significant advanced prostate cancer, maintaining castrate testosterone levels has been shown to improve survival. Retrospective trials have now addressed the adequacy of testosterone suppression for patients with biochemical failure (ie, those who have failed localized therapy). In the study by Morote and colleagues[26] mentioned previously, researchers found that in patients for whom all 3 serum testosterone readings measured $<$20 ng/dL, mean AIP-free survival was 106 months. Conversely, patients with any testosterone increases between 20 and 50 ng/dL during the course of the study achieved a mean AIP-free

survival of 90 months. For patients with any breakthrough > 50 ng/dL, mean AIP-free survival was 72 months.[26] Morote and associates defined AIP as 3 consecutive PSA increases after the nadir.

To maintain castrate serum testosterone levels, the development of longer-acting LHRH depot formulations not only allows patients to avoid daily injections and surgical castration, but it also can reduce the dose required to as little as one-eighth of the daily-injection dose.[28] Currently available LHRH depot formulations can last up to 1 year.

In a multicenter, randomized, blinded study comparing a 1-month formulation of the LHRH agonist triptorelin versus the 3-month depot formulation in patients with advanced prostate cancer, all patients experienced a median PSA decline of 97% through month 9.[27,29] In the same study, the triptorelin 1-month formulation maintained mean testosterone concentrations < 50 ng/dL in 98.8% of patients, and < 20 ng/dL in 96% of patients during treatment months 2 through 9. The corresponding percentages for the 3-month formulation were 96% and 92%.[27,29]

Testosterone: How Low?

Additionally, Oefelein and colleagues have recommended that when physicians implement ADT, they should attempt to keep patients' testosterone levels as low as possible.[24] Subsequent studies have reinforced this recommendation. Recently, Perachino and associates[30] quantified the relationship between testosterone levels achieved through ADT and the risk of death. This retrospective review involved 129 consecutive patients with a histologic diagnosis of metastatic bone-only prostate cancer naive to ADT who were given 3 months of goserelin. Researchers measured testosterone and PSA levels in these patients every 3 months, for a mean follow-up of 47.5 months. Statistical analysis showed that in patients who died, the risk of death correlated directly with Gleason score ($P < .01$), 6-month PSA level ($P < .01$), and 6-month serum testosterone level ($P < .05$; hazard ratio [HR] 1.32). These authors write that, to their knowledge, their report is "the first of a direct statistical correlation between the risk of death and testosterone levels achieved during ADT in patients with metastatic prostate cancer."[30]

Perachino and colleagues found that, although pretreatment testosterone level did not predict survival, there was a continuous relationship between testosterone level and cause-specific survival during treatment. Pretreatment Gleason scores and 6-month PSA levels being equal, "The lower the 6-month testosterone level, the longer the survival."[30]

In the Perachino analysis, of 162 men with metastatic prostate cancer on IADT with goserelin, multiple factors were analyzed, and the authors found that survival directly correlated with baseline PSA ($P < .01$), as well as with 6-month serum testosterone level ($P = .0286$). The lower the serum testosterone, the longer a patient survived.[31]

Although the success of IADT depends on restoring a normal testosterone level, it is believed that keeping testosterone levels as low as possible while patients are on treatment results in the lowest possible serum PSA levels and likely improves outcomes.[32]

Failure to Achieve Castrate Levels

Although most men undergoing continuous ADT with LHRH analogues achieve castrate levels, there is a population that does not. Various reports estimate this proportion at 13% to 42% when using a cutoff of < 50 ng/dL.[33-38] For example, Oefelein and Cornum reported that 5% and 13% of patients on 3-month depot LHRH agonist therapy failed to achieve castrate levels of 50 and 20 ng/dL, respectively. Accordingly, they concluded that standard dosing of LHRH agonists appears inadequate in some men, and that physicians must monitor serum testosterone response to LHRH therapy.[33] Failure to achieve testosterone suppression may be attributable to the following factors:

- Inadequate drug pharmacokinetics secondary to obesity
- Mutant receptor changes of the anterior pituitary
- Excess adrenal steroidogenic production of testosterone
- The impact of microsurges, also known as the acute-on-chronic effect

Furthermore, based on reports of leuprolide acetate depot formulations and goserelin implants, as well as a review by Tombal and Berges, 2% to 17% of patients fail to achieve serum testosterone < 50 ng/dL; 13% to 38% fail to achieve serum testosterone lower than 20 ng/dL.[39] These relatively elevated serum testosterone levels may have implications regarding prostate cancer progression, and ultimately may impact eventual prostate cancer–related death.

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Hence, patients who initially respond to LHRH analogues might not maintain adequate testosterone suppression at all time points. The importance of more frequent monitoring of serum testosterone cannot be overstated.

Nearly all men undergoing continuous ADT for advanced prostate cancer eventually develop androgen resistance and disease progression.[40] Patients with high-grade disease who undergo continuous androgen ablation will oftentimes experience disease progression within 2 to 3 years.[41] In men with metastatic prostate cancer, median time to androgen independence may be 18 to 24 months.[42] Although normal prostatic epithelial cells cannot regenerate and grow in an androgen-deprived state, prostate cancer cells will usually acquire an androgen-independent phenotype that can facilitate growth while androgen-deprived by traditional therapy. Most cells maintain some androgen sensitivity. Thus the term CRPC has replaced the term AIP.

However, the aforementioned phenomenon does differ from the acute-on-chronic effect, a term that characterizes testosterone surges that occur upon readministration of an LHRH agonist drug. This effect occurs in 4% to 10% of patients treated with standard LHRH therapy.[43,44] Testosterone surges or breakthroughs also can occur at any time during treatment (eg, independent of LHRH readministration).[4]

In an open-label, randomized trial of goserelin, up to 23% of men treated with goserelin escaped from castrate level ($T \leq 18.5$ ng/dL).[45] In a review of several LHRH studies, reports have estimated breakthroughs in 2% to 30% of patients on treatment.[46,47]

Obesity may also impact a patient's response to ADT. Although obese men may have lower pretreatment serum testosterone levels, they have higher total and free testosterone levels during leuprolide treatment in comparison with men with normal body mass index (BMI). Investigators have postulated that this disparity may contribute to an association between obesity and increased prostate cancer mortality.[48] Thus, BMI may also impact response to LHRH therapy. Testosterone breakthrough has been reported in 1 obese patient in a leuprolide gel study,[44] which suggested that weight-based dosing might be appropriate. Recently discovered polymorphisms in LH also could account for variable responses to LHRH analogues in women, although research has yet to confirm these polymorphisms in men.[49]

Changes in Androgen Receptor Sensitivity

Prostate cancer cell lines may be affected by testosterone-dependent and testosterone-independent milieu. In the former, testosterone and DHT stimulate proliferation via the androgen receptors. Depriving testosterone-dependent prostate cancer cells of hormones halts their growth, thereby reducing prostate cancer growth.

More than 80% of patients with advanced prostate cancer respond to ADT.[14] Along with regression of primary and metastatic disease and decreasing PSA levels seen with ADT, these patients may experience relief of symptoms such as urinary obstruction and bone pain. For patients undergoing continuous ADT, this response lasts an average of 24 months,[50] after which a rising PSA level indicates that the patient may no longer be responding to treatment. At this biochemical juncture, called testosterone "escape," it is hypothesized that cell proliferation has achieved independence from hormonal stimulation mechanisms. It is important in these patients to document that the testosterone levels are in the castrate range.

Multiple mechanisms may be responsible for androgen insensitivity. One theory states that continuous ADT eliminates testosterone-sensitive cells until a predominance of resistant cells emerges. In particular, the clonal selection hypothesis proposes that pre-existing androgen-independent cells survive and grow despite androgen deprivation.[51] Another theory, the molecular adaptation hypothesis, posits that ADT may upregulate androgen-repressed adaptive mechanisms capable of aborting apoptosis.[52-54] Conversely, IADT suppresses sensitive cells before they become resistant. Then, off-treatment periods allow androgens to return, thus repopulating the tumor with androgen-sensitive cells and allowing for a prolonged response to treatment.[10]

Some preclinical and clinical research has shown that IADT prolongs the time to androgen independence. It is theorized that the restoration of androgen levels permitted by IADT restores the apoptotic potential of the androgen-dependent tumor cells that have survived androgen deprivation, thus delaying the development of androgen independence.[11,55]

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Data regarding testosterone recovery in patients on IADT are variable, although a small study has shown that within 2.5 years of stopping therapy, nearly half of the 15 men on long-term ADT (mean duration: 6 years) had greater-than-castrate

testosterone levels.[56] Nevertheless, all but 1 of these patients maintained testosterone levels that were below normal.

IADT Definition Evolving

Currently, there is no standardization among IADT studies, which makes it difficult to compare and contrast their resulting data and conclusions. However, studies seem to follow a consistent IADT schema: researchers monitor serum PSA levels while patients are receiving ADT, then halt treatment when patients achieve a desired PSA level; while patients are no longer receiving ADT, researchers monitor PSA until it rises to a predetermined level, at which point treatment resumes. These cycles continue until clinical or PSA progression appears.[14]

Southwest Oncology Group (SWOG) 9346 may provide a definitive answer regarding the utility of IADT. This phase III trial has enrolled 1500 patients with stage D2 prostate cancer and a pretreatment PSA of $\geq$ 5 ng/mL. Per study protocol, patients underwent a 7-month induction period with goserelin and bicalutamide. After this period, patients with stable or declining PSA levels of $\leq$ 4 ng/mL were randomized to continuous ADT or IADT. Patients in the IADT group remained off treatment until PSA began to rise above their baseline levels, $>$ 20 ng/mL, or above a point determined by the investigator's discretion. Early data regarding PSA normalization rates indicate that PSA fell into the normal range ($<$ 4 ng/mL) during the induction cycle for 84% of 527 patients.[32] Final results for SWOG 9346 are pending.

Meanwhile, an interim report on the European phase III randomized trial of IADT versus continuous ADT (RELAPSE study) has shown that at 31-month follow-up, researchers found no difference between 96 patients receiving IADT and 78 patients receiving continuous ADT.[57] Similarly, interim results from a multicenter phase III German study comparing IADT versus continuous ADT with goserelin acetate and bicalutamide (AUO AP 17/95) has shown that at a median follow-up of 50.5 months, survival and time to progression were comparable in both treatment arms.[58]

An earlier study randomized 68 patients with advanced prostate cancer to IADT or continuous ADT with goserelin acetate and flutamide. After a median follow-up of 30.8 months, these investigators observed a substantially lower rate of progression to androgen independence in the intermittent arm.[59] Additionally, in a randomized European feasibility study (EC 507) involving 150 patients with PSA relapse following radical prostatectomy, investigators have detected no difference in time to progression for men on continuous or intermittent ADT to date.[19]

Although evidence suggests that IADT performs at least as well as continuous ADT in terms of survival, and perhaps better in terms of side effects, IADT still remains experimental and unproven regarding long-term implications of disease progression and survival impact.

IADT Monitoring

IADT researchers uniformly agree regarding the need to monitor testosterone levels of patients receiving these therapies. "A reasonable option to detect . . . breakthrough increases would be to monitor testosterone levels at PSA determination. Apart from having prognostic implications, knowing the level of testosterone would allow reducing the LHRH agonist accordingly" and the consideration of maximal androgen blockade, according to Gomella.[4]

However, anecdotal surveys have demonstrated that only a minority of clinicians regularly monitor serum testosterone levels. Whether patients maintain persistent castrate levels of testosterone is usually not monitored immediately before and after subsequent LHRH redosing, and few studies have examined this monitoring over long-term follow-up.

A survey conducted at a recent prostate cancer consensus meeting revealed that only 3% of attendees always measured ADT patients' serum testosterone levels; 21% did so at least once; 50% measured serum testosterone only in the event of a PSA rise, and 26% never measured serum testosterone.[25]

Notwithstanding the importance of monitoring serum testosterone levels for patients undergoing IADT, the majority of studies to date appear to support basing the decision to resume therapy on PSA levels rather than on testosterone levels. Early data from SWOG 9346 show that in patients with metastatic prostate cancer, Hussain and colleagues found that a PSA level $\leq$ 4 ng/mL after 7 months of ADT was a strong predictor of survival. "This was the first trial in newly diagnosed metastatic PC to show unequivocally the survival advantages associated with absolute PSA value in response to ADT," concluded the authors.[32]

Although evidence suggests that IADT performs at least as well as continuous ADT in terms of survival, and perhaps better in terms of side effects, IADT still remains experimental and unproven regarding long-term implications of disease progression and survival impact.

Similarly, one of the largest analyses evaluating PSA endpoint as a surrogate for overall survival in men with metastatic disease concluded that PSA endpoint could not be statistically validated as a surrogate for overall survival, but PSA normalization was a strong prognostic factor for survival.[60] Other published reports investigating the prognostic value of PSA response to ADT in hormone-naive patients consistently show a significant correlation between PSA response and time to progression and overall survival.[61-64]

Moreover, EORTC 30891 compared immediate versus delayed ADT in T0-4 N0-2 M0 prostate cancer. This study showed not only that patients with baseline PSA $>$ 50 ng/mL faced a 3.5-fold higher risk of prostate cancer death than patients with baseline PSA $\leq$ 8 ng/mL, but also that timing of PSA relapse after response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA also may reflect disease aggressiveness.[18] PSADT also appeared to play a role, as patients with baseline PSA $<$ 50 ng/mL and PSADT $>$ 12 months often died of causes unrelated to prostate cancer and therefore could be spared immediate ADT (and perhaps could be candidates for IADT). Conversely, patients with baseline PSA $>$ 50 ng/mL and PSADT $<$ 12 months faced a higher risk of death from prostate cancer and might have benefited from immediate ADT.

General Recommendations

Based on randomized studies, continuous ADT appears appropriate for patients with advanced, metastatic prostate cancer. IADT may be appropriate for many patients who reach castrate testosterone levels (T $<$ 20 ng/dL) and a PSA nadir of $<$ 4 ng/mL during induction therapy; investigators tend to randomize patients who do not reach these benchmarks to continuous therapy. Additionally, some investigators have suggested IADT for patients with biochemical failure without evidence of a local or systemic recurrence, and as an adjunct to radiation therapy for high-risk localized disease.[65] The patients most likely to benefit from IADT include those with biochemical failure and rapidly rising PSA after radiotherapy or surgery.[66] IADT may allow flexibility in achieving the survival benefits of immediate/continuous therapy while balancing the potential long-term side effects and expense of continuous therapy.

Moreover, a growing body of evidence supports initiating treatment at the time that locally advanced or metastatic disease is diagnosed rather than delaying IADT until symptomatic progression or some other occurrence.[66] Benefits of early IADT initiation in advanced prostate cancer may include prolonged time to progression and improved survival.[1]

If clinicians choose to use IADT, the initial period of androgen deprivation should last an average of 6 to 9 months—and QoL in the off-treatment phase appears improved in comparison with patients who are on treatment.[13] Additionally, studies have demonstrated that poor candidates for IADT include patients with initially bulky tumors, numerous positive lymph nodes or extensive bone metastases, baseline serum PSA levels $>$ 100 ng/mL, rapid PSA progression, or existing bone pain. Such patients frequently achieve only partial or short-term response with continuous ADT.[67]

Several strategies exist for managing the side effects of ADT. For example, ED might respond to phosphodiesterase inhibitors, vacuum devices, or intracavernous therapy.[68] Hot flashes, experienced by about 60% of men on LHRH agonists,[69] might respond to low-dose estrogens, megestrol acetate, medroxyprogesterone acetate, and cyproterone acetate.[70] Additionally, there are newer agents such as selective estrogen receptor modulators (SERMs), which may also be effective in treating hot flashes as well as ADT-induced bone loss. Of note, none of the aforementioned therapies for the treatment of ADT-induced side effects are US Food and Drug Administration approved.

As for chronic ADT adverse events, men experiencing androgen deprivation face a higher risk of osteoporosis and associated skeletal-related events. Moreover, skeletal metastases predispose men with advanced prostate cancer toward fractures. However, analysis showed that physicians rarely discuss bone-related side effects of ADT with patients, or how to prevent or minimize them.[71] Appropriate lifestyle changes for such patients include lowering alcohol consumption, smoking cessation, daily calcium and vitamin D supplements, and regular performance of resistance exercises. Resistance exercises also can counteract the progressive muscle loss associated with declining testosterone levels.

Experts have recommended checking bone mineral density of patients on ADT on a regular basis,[72] and prescribing supplemental calcium and vitamin D, as well as promoting regular exercise for all patients on ADT. Bisphosphonates are recommended for patients on ADT with bone metastases. Recent studies are also investigating a novel monoclonal antibody (denosumab) as well as a SERM (toremifene) for protecting against the osteoporotic effects of ADT. Men on ADT may also require enhanced vigilance regarding cardiac abnormalities and anemia, as well as depression, all of which have been associated with ADT use.[68]

Conclusions

The data supporting IADT are indeed promising. Although this strategy certainly merits consideration for patients with biochemical failure after localized disease therapy, it will not become the standard of care without the publication of additional large, randomized trials that support its effectiveness and identify optimal IADT candidates and protocols.

The patient who is a potential candidate for IADT should have minimal metastatic burden, should be treated with at least 6 to 9 months of induction, and then be off therapy if the PSA level is < 4 ng/mL, and preferably < 0.2 ng/mL. The timing of off-treatment periods is variable. As suggested by recent trials, testosterone levels should be < 20 ng/mL for both continuous ADT and IADT, and T levels should be monitored frequently.

The potential advantages associated with IADT—potential decrease in side effects and improvement of patient convenience and overall health care expense—must be measured against the historical understanding of disease progression and survival associated with traditional continuous ADT. ■

Dr. Crawford has served as a consultant for Elegen; a lecturer for Watson, Endo, GlaxoSmithKline, Oncura, Endocare, Ferring and sanofi aventis; and has received grant support from the National Institutes of Health and the University of Colorado Cancer Center.

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Main Points

- Although evidence for intermittent androgen deprivation therapy (IADT) has been reported to date, trials have been small and underpowered. Most clinical trials with IADT have been single-institution phase II studies. Should the evidence become more robust, the concept of IADT may become more widely accepted.
- Factors and potential outcomes that justify further research into IADT include the establishment that intermittent chemical castration may reduce the morbidity caused by long-term hormonal therapy and may ameliorate quality-of-life (QoL) issues associated with traditional ADT. Studies demonstrate that ADT-free periods give patients improved QoL, which is seen in an improved libido, sexual potency, and an enhanced sense of well-being versus maintenance on continuous ADT.
- The progression-free survival benefit of continuous ADT comes with associated adverse events. Side effects may include hot flashes, decreased libido, erectile dysfunction, loss of bone mineral density, and mood alterations. Also possible are fatigue, gynecomastia, and anemia, as well as depression and cognitive dysfunction, metabolic syndrome, and elevated risks for cardiovascular morbidity and mortality.
- Although evidence suggests that IADT performs at least as well as continuous ADT in terms of survival, and perhaps better in terms of side effects, IADT still remains experimental and unproven regarding long-term implications of disease progression and survival impact.
- Although the success of IADT depends on restoring a normal testosterone level, it is believed that keeping testosterone levels as low as possible during a patient's treatment results in the lowest possible serum prostate-specific antigen (PSA) levels and may improve outcomes.
- Based on randomized studies, continuous ADT appears appropriate for patients with advanced, metastatic prostate cancer. IADT may be appropriate for many patients who reach castrate testosterone levels ($T < 20$ ng/dL) and a PSA nadir of < 4 ng/mL during induction therapy.
- The potential patient candidate for IADT should have minimal metastatic burden, should be treated with at least 6 to 9 months of induction, and then be off therapy if the PSA level is < 4 ng/mL, and preferably < 0.2 ng/mL. Timing of off-treatment periods is variable. As suggested by recent trials, testosterone levels should be < 20 ng/dL for both continuous ADT and IADT, and T levels should be monitored frequently.

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