Intermittent Androgen Suppression as a Treatment for Prostate Cancer: A Review

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ABSTRACT
Prostate cancer continues as the most common malignancy in men in the United States, with a large number of patients presenting with advanced disease. The current treatment for metastatic prostate cancer, permanent androgen withdrawal, is palliative. Patients treated with permanent androgen withdrawal usually relapse and die secondary to prostate cancer’s ability to progress to an androgen-independent state of growth. Based on preclinical studies and phase II trials, intermittent androgen suppression (IAS) appears to be a potential alternative to permanent androgen withdrawal.

IAS may be a feasible alternative for the treatment of metastatic prostate cancer. In this paper, preclinical studies that form the basis of IAS and the clinical studies to date concerning IAS are reviewed. Through the cycling of reversible androgen suppression, there appears to be recovery of apoptosis and subsequent slower progression to an androgen-independent state. The small clinical studies conducted to date show the feasibility of IAS, and, in a few studies, there appears to be a survival advantage over historic controls. A prospective randomized trial which is currently under way will test IAS as a treatment alternative in stage D2 prostate cancer. The Oncologist 1998;3:419-423

INTRODUCTION
The American Cancer Society estimates that approximately 15% of American men will develop prostate cancer during their lifetime [1]. In 1997, based on revised projections, prostate cancer will be diagnosed in an estimated 209,000 American men, and 41,000 will die of the disease. Prostate cancer continues to be the most common malignancy in men and the second leading cause of cancer death [2, 3]. Prostate cancer accounts for 36% of all male cancers in the United States and 13% of cancer-related deaths in men [2, 3]. The highest mortality rate of prostate cancer is observed in black men, who have twice the death rate of white men [2, 4]. Between 1976 and 1994, the overall incidence of prostate cancer doubled, and the mortality increased by 20% [5]. Over a six-year period, 1992-1998, there was a dramatic increase in the incidence of prostate cancer within the United States [2, 6]. This increased incidence is mostly attributed to introduction and widespread application of prostate-specific antigen (PSA). Staging data during that same time period have shown a shift to an earlier stage of prostate cancer at time of diagnosis with a resultant increase in the five-year survival rate [6]. Notwithstanding the apparent advances in diagnosis and therapeutic approach of prostate cancer, mortality from prostate cancer has not decreased. In fact, the therapeutic approach for men with Stage D2 prostate cancer, namely androgen withdrawal, has become the predominant and exclusive mode of therapy since its introduction more than 50 years ago.

Historically, endocrine ablative therapy is rooted in observation made centuries ago. A relationship between testicular factors and prostate growth was first studied by John Hunter in 1786 [7], although he did not relate his observations to endocrine factors. Berthold in 1849 [8] did assume a relationship between testicular endocrine factors and prostate growth. Androgen withdrawal was first incorporated by several nineteenth-century physicians using castration as a treatment for patients with an enlarged prostate gland [9, 10]. The practice of androgen withdrawal was truly accepted following the work of Huggins and colleagues in the early 1940s at the University of Chicago [11, 12]. Huggins et al. showed that in patients with metastatic prostate cancer, estrogen or castration...
dramatically improved clinical symptomatology in a significant proportion of patients as well as decreased serum levels of acid phosphatase. The group established that these beneficial effects were due to androgen deprivation by observing increases in acid phosphatase and pain after injecting castrated patients with testosterone [11, 12].

Androgen ablative therapy can be achieved by a variety of methods. Historically, orchietomy is the most direct and simplest mode of ablating the major source of testosterone in man. At the present time, the majority of men with prostate cancer who undergo androgen ablation do so pharmaceutically with drugs that inhibit the synthesis and peripheral action of testosterone. Yet, despite a high initial response rate of 70%-80% of patients with disseminated disease to the initiation of complete androgen withdrawal, the benefit of such therapy has been temporary and palliative [13-15]. The median survival with metastatic prostate cancer ranges between two and three years [13-15]. Some authors have argued that measurable criteria are not valid assessments of response in prostate cancer because the goal of therapy in this setting has been palliative [16]. Because of the known adverse side effects and toxicities of complete androgen deprivation with men, quality of life as well as duration of survival should be assessed in determining effectiveness of therapy.

In this manuscript, we will review the theories and rationale of intermittent androgen suppression (IAS) and the animal and human studies that support the concept of IAS.

**Concept of IAS**

The functional unit of the prostate is the glandular acinus that consists of both epithelial and stromal elements [17]. The epithelial component includes secretory epithelial cells, basal epithelial cells, and neuroendocrine cells, as well as macrophages and lymphocytes [18]. Secretory epithelial cells are androgen-dependent for growth and thus contain androgen receptors on their surface. When androgens are withdrawn, these cells involute through the activation of a cell death program, apoptosis [18]. It is important to note that only glandular epithelial cells undergo apoptosis upon androgen withdrawal, and not basal or stromal cells [19].

Apoptotic regression in an androgen-dependent tumor can be induced by a procedure which reduces the intracellular concentration of dihydrotestosterone in the prostate gland by more than 80% [20, 21]. The concept underlying the progression of prostate cancer, despite complete androgen withdrawal, relates to a clonal evolution of cells within the tumor that are androgen-independent. It is possible that permanent androgen deprivation might even promote androgen-independent growth and progression. The concept of androgen independence was studied by Robert L. Noble using a tumor hormone-dependent breast cancer in the Nb rat [22]. Noble’s studies showed a delay to hormone independence with a moderate reduction in hormone levels, as opposed to complete deprivation of hormone by castration. Bruchovsky et al. were able to show that androgen-dependent cells are capable of undergoing adaptive changes rendering them androgen-independent [23]. Applying the androgen-dependent Shionogi carcinoma as a model (using androgen withdrawal through means of castration), they found the ratio of stem cells in the tumor population was altered. Following androgen withdrawal, Bruchovsky et al. not only found a twenty-fold increase in the proportion of total stem cells, but a 500-fold increase in the proportion of androgen-independent stem cells. This experiment implies that the transformation of surviving clonogenic tumor cells (stem cells) from an androgen-dependent phenotype into an androgen-independent phenotype is induced by the cessation of androgen-dependent cell growth in the primary tumor. However, according to this model, if androgen suppression therapy is withdrawn before progression of clonogenic tumor cells to an androgen-independent state, the surviving clonogenic cells should continue to be androgen-dependent, and the prostate cancer could be still amenable to treatment by subsequent androgen blockade. This cycling of complete androgen ablation followed by its cessation and the resultant increase in serum testosterone form the basis of IAS.

**IAS: Preclinical Studies**

Akakura and colleagues were able to induce multiple apoptotic regressions using IAS [24]. To illustrate the effect of intermittent androgen exposure, they successively castrated and transplanted the androgen-dependent Shionogi carcinoma into a succession of male mice. The cycles of transplantation and castration-induced apoptosis were repeated four times until growth became androgen-independent, which occurred during the fifth transplantation. Their results showed that mean time to androgen independence with complete permanent androgen cessation was only 50 days, compared with 150 days using IAS. Further animal studies were performed using IAS in LNCaP and Shionogi tumor models, which suggested time to androgen independence is prolonged threefold [25] from 24 days to 75 days in the IAS group. This model continued to support the concept that progression to an androgen-independent state may result from adaptive changes of the tumor cell and upregulation of androgen-repressed growth regulatory pathways. There were several animal studies performed in the 1980s that showed equivocal results associated with IAS [26, 27]. In 1980 and 1985, Vahlensieck et al. [28, 29] reported that with advanced prostate cancer, the use of intermittent oral therapy with estramustine phosphate failed to show a significant difference in terms of clinical response. These studies did not utilize PSA as a marker to monitor intervals of remission and progression.
An obvious concern of taking IAS into the clinic was that acute signs and symptoms of "tumor flare" might result from IAS if serum testosterone levels abruptly returned to normal. However, if serum testosterone levels slowly returned to normal over a period of weeks or months, in theory no tumor flare should occur. The theory is that by using testosterone withdrawal and its slow restoration, it is more likely that the androgen dependency of prostate cancer will be maintained. Thus, IAS would initially produce apoptosis in the androgen-dependent clonogenic prostate cancer cells. The cessation of androgen blockade would rescue some of the androgen-dependent clonogenic cells and restore hormone dependence. The rest effect of IAS could in turn be followed by the serum PSA and the length of time it took to become elevated.

**IAS: Clinical Studies**

The concept of IAS for the treatment of metastatic prostate cancer has only recently begun to be investigated in human studies. IAS may decrease toxicity and improve quality of life when compared with continuous androgen ablation. Additionally, based on the preclinical models, IAS might lead to a better overall survival. However, these hypotheses remain to be proven. Prior to the introduction of PSA, there were very few clinical trials to study the concept of IAS. For the concept of IAS to be utilized in prostate cancer, there must be the availability of reversible agents for androgen deprivation (i.e., LHRH analogs and antiandrogens) as well as a tumor marker (i.e., PSA).

Klotz et al. [30] treated nineteen patients with advanced prostate cancer using diethylstilbestrol (DES) in an intermittent endocrine therapy schedule. Duration of endocrine therapy prior to withdrawal lasted an average of 10 months. The treatment-free interval lasted a median of eight months. During the time off DES, patients reported improved quality of life. Nine of ten patients rendered impotent by DES therapy resumed sexual activity. All patients who relapsed had a rapid clinical response following resumption of DES.

Akakura et al. [24], in addition to their studies involving the Shionogi carcinoma, initiated androgen withdrawal in four stage C and three stage D patients with prostate cancer using PSA as a tumor marker. The cycles were repeated sequentially for a total of two to four times over treatment periods of 21-47 months without loss of androgen dependence.

The largest clinical experience published to date involved 47 patients (clinical stage D2: 14; D1: 10; C: B2: 2; and A2: 2) in British Columbia using IAS [31]. PSA was utilized as a marker to monitor disease progression and regression. Combined androgen suppression consisting of either cyproterone acetate (100 mg/day) and low-dose DES (0.1 mg/d) or an LHRH agonist plus an antiandrogen was initiated and continued for at least six months until a stable PSA nadir was reached. At that point, treatment was then withheld and the patient was observed. Treatment of androgen blockade was reinstated when the PSA level climbed back to a mean value between 10 and 20 mg/ml (average 14 ng/ml). This cycle of treatment and no treatment was repeated until the regulation of serum PSA became androgen-independent. On this schedule, androgen dependence appeared to be maintained for at least two cycles (up to five cycles). One cycle consisted of the sum of treatment plus the time off treatment. The first two treatment cycles lasted 73 and 75 weeks with an overall mean percentage time off therapy of 41% and 45%, respectively. In 7 of 14 patients with stage D2 disease, the cancer progressed to an androgen-independent state. The mean and median overall survival of 210 weeks and 166 weeks were comparable with historical series. The mean cancer-specific survival time was 232 weeks. The results did show a large difference in median survival for patients achieving a nadir PSA <32 weeks, suggesting the subset of patients not obtaining these values should be considered for other therapies. Testosterone returned to a normal range within eight weeks of stopping treatment. The off-treatment period was associated overall with an improvement of sense of well-being and the recovery of libido and potency (in the men who reported normal or near-normal sexual function before the start of therapy).

Higano et al. [32] performed a clinical study at the University of Washington using IAS. Twenty-two patients with PSA failure following primary therapy with surgery and/or radiation therapy and patients with untreated early or stage D2 disease were treated. Leuprolide and flutamide were administered for nine to 12 months and then discontinued once the PSA value reached a threshold value that was determined by the baseline PSA value. In this feasibility study, 21/22 patients completed treatment with a mean time to nadir of three and one-half months. Fifteen patients completed their off-treatment period of six months (median percentile of 38% of cycle off treatment). Six of 21 were still off treatment in cycle number one with stable disease. During cycle two, 12 of the available 15 patients achieved a PSA nadir in a median time of 3.5 months. Two patients had completed cycle two with a median time off treatment of 10 months (51% time off treatment). Ten patients were still on treatment in cycle number two receiving endocrine therapy. Of the seven patients with stage D2 disease, six patients are still actively cycling (one patient chose not to proceed with the study). Four of the patients with stage D2 disease had completed cycle one with a median percentage time off treatment of 35.5% (two patients were still off treatment). Of the six still actively cycling at a median time of 22+ months (range 19+ to 35+ months), there is no evidence of hormone refractory disease.

All patients included in this study reported a reduction of symptoms associated with androgen suppression. All patients
who cycled off treatment for at least three months noted an improvement in overall quality of life. Clinical improvements were noted with the reversible effects of androgen suppression on diabetes, hypertension, weight gain, hot flashes, energy level, and neuropsychic symptoms, as well as potency and libido (overall 14/15 experienced increased libido; at least three patients were impotent before starting treatment, but all noted improved libido off treatment).

Tunn et al. [33] evaluated 20 patients with a low tumor burden with a mean follow-up of 28 months. The median time off treatment was 36 weeks, which is 45% of the complete cycle. In their study, no patient had progressed to an androgen-independent tumor state during the evaluated observation time of 28 months.

Oliver et al. [34] performed a retrospective review of a series of patients who by design or chance had stopped endocrine treatment following a documented tumor marker complete remission. They reported on 20 patients, seven M+ and 13 M0 (6 T3M0 and 7 <T3M0). Seven of 20 patients continue progression-free for 9 to 42 months. Thirteen relapsed after a median observation of nine months. Ten of these 13, after second-line hormone therapy, remain progression-free at two years. Progression-free survival was lower in patients with metastatic disease (29% at one year) versus M0 disease (82% at one year). Overall, 45% of patients showed no progression, 10 of 13 patients demonstrated an ongoing PSA response, while 85% were alive at three years. Of the seven patients with metastatic disease, two died during the second hormone treatment, four patients are currently cycling with the second hormone treatment, and one patient remains off hormone therapy +33 months from stopping initial hormone therapy.

The results of the aforementioned pilot studies are shown in Table 1. The salient points of the studies to date are that the length on IAS is roughly equivalent to the time off, despite the fact that testosterone production usually begins with the first three to four months off therapy. While many of the studies have limited follow-up, there does not appear to be a survival disadvantage to this approach. Many of these feasibility studies have reported death from events other than prostate cancer, and given the fact that many of the patients treated to date are elderly with comorbid disease, this is not surprising.

### Table 1. Report results of intermittent androgen suppression (IAS)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Duration of IAS</th>
<th>Time to progression</th>
<th>Median time off</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz/86</td>
<td>19</td>
<td>Advanced</td>
<td>10 months</td>
<td>8 months</td>
<td>44%</td>
<td>NYR&gt;24 months</td>
</tr>
<tr>
<td>Akakura/93</td>
<td>7</td>
<td>C + D</td>
<td>8.5 months</td>
<td>7 months</td>
<td>39%</td>
<td>NYR&gt;60 months</td>
</tr>
<tr>
<td>Goldenberg/95</td>
<td>47</td>
<td>A2-D1</td>
<td>43 weeks (mean)</td>
<td>30 weeks (mean)</td>
<td>41%</td>
<td>166 weeks</td>
</tr>
<tr>
<td>Higano/96</td>
<td>22</td>
<td>D2</td>
<td>9-12 months</td>
<td>6 months</td>
<td>38%</td>
<td>NYR&gt;22 months</td>
</tr>
<tr>
<td>Tunn/96</td>
<td>20</td>
<td>Not stated</td>
<td>9 months</td>
<td>&gt;9 months</td>
<td>45%</td>
<td>NYR&gt;28 months</td>
</tr>
<tr>
<td>Oliver/97</td>
<td>20</td>
<td>D2 + C2</td>
<td>9 months</td>
<td>9 months</td>
<td>50%</td>
<td>85% @ 36 months</td>
</tr>
</tbody>
</table>

NYR = not yet reached.

### CONCLUSION
Prostate cancer continues as an urgent health problem in the United States. In this paper, we presented an overall review of the preclinical data and feasibility studies performed to date on IAS. IAS has been shown to be feasible, and the preliminary studies show that it is equivocal and possibly superior to permanent androgen blockade. IAS should cost less and may offer reduced overall toxicity and an improved quality of life for the man with metastatic prostate cancer. There has now been initial evidence that IAS may lead to an improved overall survival. Some studies have shown that IAS is less successful in patients with high tumor burden. By treating prostate cancer with intermittent cycles of on and off hormone therapy, there is an increased recovery of apoptotic potential. This cycling of periods with and without androgen suppression provides the prolongation of an androgen-dependent state and seems essential to slowing down tumor progression.

There also exists the possibility of alternating androgen suppression with other treatment modalities. As encouraging as the data are, only after a prospective randomized trial of continuous versus IAS with formal quality of life questionnaires can we establish whether quality of life and survival are significantly improved.

Furthermore, the optimal duration of IAS remains to be determined. A trial is currently being conducted as an Intergroup Trial (Southwest Oncology Group, and Cancer and Leukemia Group B) in patients with newly diagnosed stage D2 prostate cancer. An integral part of the study is a prospective assessment of quality of life. In the meantime, accurate screening and overall awareness for prostate cancer should be maintained, and improved diagnosis and treatment modalities must continue to be explored.
REFERENCES