Intermittent Androgen Deprivation in Prostate Cancer Patients: Factors Predictive of Prolonged Time Off Therapy

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Key Words. Prostate cancer · Androgen-deprivation · Intermittent hormone therapy

ABSTRACT

Objectives. We hypothesize that prostate cancer (PC) patients who achieve and maintain an undetectable prostate-specific antigen (UD-PSA) on androgen deprivation therapy (ADT) have a predominantly androgen-dependent cancer cell population sensitive to apoptosis that allows for a prolonged time off ADT. This study summarizes patient- and treatment-related factors associated with a prolonged time off ADT in patients electing intermittent androgen deprivation (IAD).

Methods. Hormone-naïve patients with PC were treated with ADT using an antiandrogen and a luteinizing-hormone-releasing hormone-agonist. Of 255 consecutive patients, 216 (85%) achieved a UD-PSA (<0.05 ng/ml). Ninety-three (43%) of 216 elected to stop ADT after maintaining a UD-PSA for a median of one year. Patients were followed off therapy and advised to restart ADT if the PSA level reached \( \geq 5.0 \) ng/ml. Forty-one patients received finasteride as part of IAD induction and as maintenance off therapy; these patients are excluded from the current study and are the focus of another publication. The remaining 52 patients are assessable for response being either in the off-phase of IAD \( \geq 1 \) year or having restarted IAD.

Results. In the first IAD cycle, the median duration of the on-phase of IAD was 16 months (mean 19.0 months, range 3.6-71 months), and the median off-phase duration was 15.5 months (mean 24.1 months, range 3.2-87+ months). In 28 patients who maintained a UD-PSA for \( \geq 1 \) year, their median off-phase duration was 29 months (mean 35.8 months, range 7.8-87+ months), with nine (32%) still off IAD after a median follow-up of 62 months. Significant (\( p < 0.05 \)) independent factors associated with prolonged off-phase duration by multivariate analysis included UD-PSA on ADT \( \geq 1 \) year (\( p = 0.010 \)), PSA-only recurrence after local therapy (\( p = 0.039 \)), and reaching a testosterone level \( \geq 150 \) ng/dl in \( \geq 4 \) months off ADT (\( p = 0.041 \)). After a median of 66 months of follow-up, only one (2%) patient developed androgen-independent PC.

Conclusions. Hormone-naïve patients who achieve and maintain a UD-PSA for at least one year during ADT may initiate IAD and anticipate a prolonged off-phase duration. Attainment of a UD-PSA on ADT may serve as an in vivo sensitivity test of a patient's tumor cell population, and allow for better selection of those best suited for IAD. The Oncologist 2000;5:45-52

INTRODUCTION

The contemporary approach using androgen deprivation therapy (ADT) in advanced prostate cancer (PC) involves uninterrupted treatment. This assumes an ongoing response to therapy and the absence of significant adverse effects. Adverse effects from ADT are accepted by most men if they achieve a meaningful remission from their disease, particularly for men with advanced disease [1]. Patients with localized PC are candidates for local therapy that may include ADT [2, 3]. In such men, recent studies report a diminished quality of life during ADT [4-6]. Symptoms attributable to ADT include loss of libido, impotence, loss of muscle bulk and strength, weight gain, cognitive dysfunction and vasomotor instability. Additionally, acute and chronic complications such as anemia [7, 8] and osteoporosis [9-12] may occur, the latter of which results in greater debility than is usually recognized [12]. ADT has also been reported to exacerbate medical

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The Oncologist 2000;5:45-52 www.TheOncologist.com
conditions such as hypertension, diabetes mellitus and hyperlipidemia [6, 13].

In 1989, we began to discontinue ADT in consenting patients who achieved and maintained an undetectable prostate-specific antigen (UD-PSA). This approach was initiated due to favorable reports using intermittent androgen deprivation (IAD) [4-6, 14, 15]. Our preliminary results using this approach were published in abstract form [16-19]. The current publication presents significant patient- and treatment-related factors associated with a prolonged off-therapy duration in 52 assessable patients electing IAD.

**MATERIALS AND METHODS**

**Patients**

All patients had histologically confirmed PC and were naïve to ADT and chemotherapy. Two hundred fifty-five consecutive patients received combination antiandrogen (AA) and lutenizing-hormone-releasing hormone-agonist (LHRH-A) therapy. Thirty-nine patients (15%) did not achieve or maintain a UD-PSA on ADT; they underwent changes in therapy and are not included in this report. Of 216 patients who attained a UD-PSA, 67 (31%) with clinically localized disease elected local treatment; they are excluded from this report. Forty-seven (22%) of 216 patients met our criteria for IAD but did not consent to IAD. Eight (4%) patients were not evaluable: four were lost to follow-up, three died of a second malignancy and one expired from an acute myocardial infarction while in clinical remission.

Ninety-three (43%) of 216 patients elected to stop ADT due to side effects and after being informed of the potential risks and benefits of IAD. Of these, 41 (44%) had received finasteride during ADT induction and elected to continue finasteride as maintenance therapy while off IAD. Their responses are the focus of another publication [20]. The remaining 52 patients are in the off-phase of IAD for 1 year or restarted subsequent IAD cycles and are assessable for response.

**Patient Characteristics for IAD Therapy**

Twenty-nine untreated PC patients had clinical stages T₁c (six), T₂a-c (18) and D₀₋₂ (five). Twenty-three patients had undergone local treatment(s) and presented with PSA-only recurrence (PSAR) as the first sign of treatment failure. Four of these patients were documented to have stage D₂ PC while the remaining 19 had PSAR only. Median time from the diagnosis of PC until ADT was 12 months (mean 37 months, range 0-78 months).

**Assessments and Drug Therapy**

Baseline characteristics for the 52 assessable patients are summarized in Table 1. Patients were assessed at baseline and monthly for the first six months, and every two or three months thereafter. Over 80% of patients received flutamide (250 mg orally every 8 h) and leuprolide acetate (7.5 mg i.m. monthly) with AA begun one week before LHRH-A administration to prevent flare [21]. The remaining patients received goserelin and either bicalutamide or nilutamide. After ADT was discontinued, patients entered the off-phase of IAD and were evaluated as above. Patients were advised to restart IAD if the PSA level reached ≥5.0 ng/ml during the off-phase.

**Definitions of Terms Used**

Baseline was considered the date of the first LHRH-A injection. The number of months from baseline until a sustained UD-PSA (<0.05 ng/ml using Tosoh or Immulite assay) was reached was defined as the UD month. Thirty days after the last LHRH-A injection was defined as the stop date. A cycle of IAD was calculated from baseline until the date IAD was restarted or the date of the last office visit, whichever occurred first. The off-phase duration of IAD was calculated from the stop date until baseline of a subsequent cycle. For patients still in an off-phase of IAD, off-phase duration was calculated as of their last office visit before May 10, 1999. Testosterone recovery in the off-phase of IAD was calculated from the stop date until the date the testosterone level was ≥150 ng/dl. Forty-three patients had “low volume disease” including 19 PSAR patients and 24 with clinical stage T₁c₋T₂a₋c PC.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of 52 IAD patients</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>IAD patients assessable ≥ 1 year</td>
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<tr>
<td>Age at IAD (years)</td>
</tr>
<tr>
<td>Baseline PSA (ng/ml)</td>
</tr>
<tr>
<td>Baseline testosterone (ng/dl)</td>
</tr>
<tr>
<td>Gleason score</td>
</tr>
<tr>
<td>Prior treatment(s)</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Radical prostatectomy (RP)</td>
</tr>
<tr>
<td>External beam radiation therapy (EBRT)</td>
</tr>
<tr>
<td>RP + EBRT</td>
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<tr>
<td>Clinical stage</td>
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<tr>
<td>T₁c and T₂a₋c</td>
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<tr>
<td>D₀</td>
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<tr>
<td>D₁</td>
</tr>
<tr>
<td>D₂</td>
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<tr>
<td>PSAR</td>
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</table>
Statistical Considerations

Univariate and multivariate analyses were used to determine the prognostic value of patient characteristics and treatment-related variables. Patients still in an off-phase of IAD were censored as of their last office visit before May 10, 1999. For IAD cycle-1, time-off curves were generated by the method of Kaplan and Meier [22] and comparisons between curves were made by log-rank analysis [23]. To determine independent factors significantly contributing to a prolonged off-phase duration of IAD, the proportionate hazards (Cox) model was applied [24]. All analyses were performed using SPSS statistical package and JMP software for Macintosh. *p* values < 0.05 were considered statistically significant. All statistical tests were two-sided.

RESULTS

As of May 10, 1999, 52 PC patients received IAD with a median of 66 months of follow-up (range 28-121 months). In IAD cycle-1, the median on-phase IAD duration was 16 months (mean 19.0 months, range 3.6-71 months) and the median off-phase duration was 15.5 months (mean 24.1 months, range 3.2-87+ months). In 28 patients who maintained a UD-PSA for ≥1 year, their median off-phase duration was 29 months (mean 35.8 months, range 7.8-87+ months), with nine (32%) still off IAD after a median follow-up of 62 months (mean 59.6 months, range 19.7-87.1+ months, Fig. 1A). These nine patients had a median on-phase UD-PSA duration of 15.5 months (mean 22.4 months, range 12.7-66.4 months). In contrast, all patients with an on-phase UD-PSA duration <1 year resumed IAD after a median off-phase duration of 13.5 months (mean 16.7 months, range 3.2-43.9 months). Eight (89%) of the nine patients remaining in the off-phase of IAD-cycle-1 had low-volume disease (five with PSAR and three with clinical stage T<sub>1</sub>-T<sub>3</sub>, PC). Only one patient with clinical stage D$_2$ disease remains in the off-phase of IAD-cycle-1 after 49.8 months, but has not had testosterone recovery to ≥150 ng/dl during this period of follow-up.

Of 43 patients completing IAD cycle-1, 27 are considered evaluable for response to cycle-2. Twelve of 27 are currently in the on-phase of cycle-2, nine are in the off-phase of IAD cycle-2 and six others are currently in the on-phase of IAD cycle-3. Thirteen patients were not evaluable for response to IAD cycle-2 (seven elected local treatment, three refused LHRH-A injections and three were lost to follow-up). Three (6%) patients with clinical stage D disease failed to achieve a UD-PSA on IAD cycle-2, one of whom has androgen-independent PC (AIpc). Fifteen of 27 patients completing the on- and off-phases of IAD cycle-2 had similar PSA and testosterone responses to initiation and withdrawal of ADT as in IAD cycle-1 (Table 2).

Four (8%) of 52 patients have not reached a testosterone level ≥150 ng/dl and remain off IAD after a median follow-up of 41 months (range 44-69+ months). Compared to the 48 other patients who had testosterone recovery, these patients were significantly older (mean age 74.8 versus 65.8 years, *p* = 0.034) and were treated longer (mean ADT 34.4 versus 17.4 months, *p* = 0.15). Of 40 patients <74 years of age, two (5%) have not reached a testosterone level ≥150 ng/dl, whereas 38 (95%) had testosterone recovery after a median of 3.5 months (range 2-38 months). Of 42 patients receiving ADT <2 years (median 15 months, range 4-22 months), only two (2%) have not reached a testosterone level ≥150 ng/dl, and 40 (98%) had testosterone recovery after a median of three months (range 1-38 months). Using multivariate analysis, neither patient age nor duration of ADT were independently associated with testosterone recovery.

Patient and Treatment-Related Variables Predictive for Time Off IAD-Cycle 1

We examined the off-phase duration of IAD cycle-1 in accordance with patient- and treatment-related variables using both univariate and multivariate analyses. Variables that significantly correlated with a prolonged off-phase duration using univariate analysis included on-phase UD-PSA duration ≥12 months (*p* = 0.00002), testosterone recovery to ≥150 ng/dl in ≥4 months (*p* = 0.0049) and PSAR (*p* = 0.035) (Fig. 1A-C). On multivariate analysis, the only independent variables significantly associated with a prolonged off-phase duration were on-phase UD-PSA duration (*p* = 0.010), PSAR (*p* = 0.039) and reaching a testosterone level ≥150 ng/dl in ≥4 months (*p* = 0.041).

COMMENT

We employed IAD with the hypothesis that continuing ADT in responding patients may result in further apoptosis yielding a longer off-phase duration. This approach was also based on published reports showing responses to ADT beyond 9-12 months as well as long-term disease-free survival in subsets of patients with advanced PC receiving protracted ADT [25-28]. A meta-analysis of patients enrolled in these trials showed higher response rates and longer survival if limited stage D$_2$ was present [29, 30]. However, the high initial response rates with ADT in advanced PC patients were generally limited by eventual progression due to AIPC [29, 30]. Given the viewpoint that advanced PC patients have a limited life expectancy and potential side effects of continuous ADT could reduce quality of life, IAD appeared to be a reasonable alternative treatment approach. Previous trials that studied IAD are summarized in Table 3 together with the results of our trial.
In the present study, we evaluated 52 patients who elected to discontinue ADT. Unlike other studies [4-6], we offered IAD only to patients who achieved and maintained a UD-PSA on ADT and who elected to stop ADT due to various symptoms. We identified several patient- and treatment-related variables associated with prolonged off-phase duration of IAD cycle-1 using univariate analysis. However, on multivariate analysis, only UD-PSA on ADT ≥1 year, PSAR and reaching a testosterone level ≥150 ng/dl in ≥4 months were independently associated with a prolonged off-phase duration. Nine (17%) patients remain off IAD after a median follow-up of 62 months, all who maintained a UD-PSA during IAD cycle-1 ≥1 year and eight with low-volume disease.
Using achievement of UD-PSA as our response criteria, 20 (77%) of 26 patients assessable for IAD-cycle-2 had identical patterns of PSA response compared to cycle-1 [31]. Only 3 (4%) of 52 patients failed to achieve a UD-PSA on cycle-2, one (2%) of whom developed AIPC. Ongoing ADT responsiveness in our patient sample is consistent with results reported by other investigators using continuous ADT [32, 33]. In 179 PC patients found to have positive lymph nodes at lymphadenectomy and receiving immediate ADT, Zagars et al. showed only a 5% actuarial incidence of progression at eight years in patients who achieved a UD-PSA [32]. In a study involving 323 PC patients, Fowler et al. showed that incremental increases in the PSA nadir correlated with the time-to-disease progression on ADT [33]. Of 156 patients who achieved a PSA nadir <1.0 ng/ml, only five (3%) developed a rising PSA on ADT.

A similarly low incidence of AIPC in low-volume PC patients receiving IAD has been reported by other investigators [6, 34, 35]. A recent report by Grossfeld et al. involved 47 patients with “localized PC;” although 12 patients had clinical stage T3 disease and one had stage T4 disease [34]. All received leuprolide acetate, 33 of whom also received flutamide. ADT was given until the PSA normalized, and for PSAR patients, was given until a UD-PSA was reached or stabilized at an acceptable level. ADT was continued for one or two months thereafter, then stopped. The mean on-phase duration of IAD cycle-1 was 16 months with a mean off-phase duration of approximately eight months. The mean duration of cycle-2 was 11 months with a mean time off IAD of 5.5 months. The mean percentage off-phase was 47% for cycle-1 and 50% for cycle-2, which was similar to what we observed in our patients who required a second IAD cycle. Of note, all except one of the patients who

| Table 1. Comparison of responses in patients completing two IAD cycles
<table>
<thead>
<tr>
<th>Baseline PSA (ng/ml)</th>
<th>Cycle 1 (n = 43)</th>
<th>Cycle 2 (n = 15)</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (median)</td>
<td>Mean (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PSA (ng/ml)</td>
<td>17.1 (8.4)</td>
<td>6.6 (6.5)</td>
<td>0.157</td>
</tr>
<tr>
<td>UD month</td>
<td>5.2 (4.5)</td>
<td>4.9 (3.5)</td>
<td>0.729</td>
</tr>
<tr>
<td>On-phase duration (months)</td>
<td>17.5 (15.5)</td>
<td>17.4 (17.0)</td>
<td>0.974</td>
</tr>
<tr>
<td>Off-phase duration (months)</td>
<td>17.0 (14.0)</td>
<td>14.0 (13.0)</td>
<td>0.367</td>
</tr>
<tr>
<td>Percent of cycle in off-phase</td>
<td>48.2% (49.5%)</td>
<td>39.8% (42.3%)</td>
<td>0.077</td>
</tr>
<tr>
<td>Testosterone recovery (months)</td>
<td>4.9 (3.0)</td>
<td>4.3 (4.0)</td>
<td>0.627</td>
</tr>
</tbody>
</table>

Key to footnotes:
1Excludes three patients failing to reach a UD-PSA on IAD cycle-2, seven electing to undergo a local treatment after the on-phase of IAD cycle-2, three refusing LHRH-A injections during the on-phase of cycle-2, one expiring from an acute myocardial infarction during on-phase of cycle-2, one expiring from a second malignancy during on-phase of cycle-2 and one lost to follow-up.
2Excludes nine patients currently in the off-phase of IAD cycle-1 and 12 patients currently in the on-phase of cycle-2.
3Patients completing the on-phase of IAD cycle-2, six of whom have entered IAD cycle-3.
4Student’s 2-sided t-test, differences are considered significant if p < 0.05.

Table 2. Comparison of published IAD regimens

<table>
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</thead>
<tbody>
<tr>
<td>Type(s) of ADT used</td>
<td>DES (19)</td>
<td>DES + flutamide (1)</td>
<td>Leuprolide + flutamide</td>
<td>Leuprolide + flutamide</td>
<td>Leuprolide + nilutamide</td>
<td>LHRH-A + antiandrogen</td>
</tr>
<tr>
<td>Clinical stages and number of patients</td>
<td>n = 0</td>
<td>n = 23</td>
<td>n = 10</td>
<td>n = 11</td>
<td>n = 4</td>
<td>n = 19</td>
</tr>
<tr>
<td>PSAR</td>
<td>n = 0</td>
<td>n = 23</td>
<td>n = 10</td>
<td>n = 11</td>
<td>n = 4</td>
<td>n = 19</td>
</tr>
<tr>
<td>A-C</td>
<td>n = 20</td>
<td>n = 24</td>
<td>n = 10</td>
<td>n = 24</td>
<td>n = 11</td>
<td>n = 24</td>
</tr>
<tr>
<td>D</td>
<td>n = 20</td>
<td>n = 24</td>
<td>n = 10</td>
<td>n = 24</td>
<td>n = 11</td>
<td>n = 24</td>
</tr>
<tr>
<td>Baseline PSA (mean)</td>
<td>N/S</td>
<td>158.0 ng/ml</td>
<td>20.0 ng/ml</td>
<td>24.5 ng/ml</td>
<td>37.0 ng/ml</td>
<td>26.1 ng/ml</td>
</tr>
<tr>
<td>ADT duration (mean)</td>
<td>29.7 months</td>
<td>9.9 months</td>
<td>9.0-12.0 months</td>
<td>9.0 months</td>
<td>8.0 months</td>
<td>19.0 months</td>
</tr>
<tr>
<td>Off-phase (mean)</td>
<td>7.8 months</td>
<td>6.9 months</td>
<td>6.0 months</td>
<td>6.0 months</td>
<td>35.0 weeks</td>
<td>24.1 months</td>
</tr>
<tr>
<td>% of cycle in off-phase</td>
<td>43%</td>
<td>41%</td>
<td>36%</td>
<td>40%</td>
<td>40%</td>
<td>49%</td>
</tr>
<tr>
<td>Number (%) of patients completing cycle-1</td>
<td>12/20 (60%)</td>
<td>30/47 (64%)</td>
<td>15/22 (68%)</td>
<td>25/35 (71%)</td>
<td>50/54 (92%)</td>
<td>43/52 (83%)</td>
</tr>
</tbody>
</table>

Key to footnotes:
1DES = diethylstilbestrol.
2N/S = not stated since the study pre-dated the availability of PSA testing.
responded to IAD cycle-1 in that study failed to respond to IAD cycle-2 after a mean follow-up of 24 months (range 5-52 months).

Initiating ADT earlier, when the tumor burden is less, should theoretically decrease the probability of AIPC arising as PC cells possibly mutate during continued tumor progression. Moreover, achievement and maintenance of a UD-PSA <0.05 ng/ml may be a valid means to discriminate patients with androgen-dependent PC (ADPC) from those harboring AIPC, since only one patient in our study developed AIPC. ADT, therefore, may serve as an in vivo sensitivity test of the tumor cell population to select out patients with probable AIPC who are likely to be better candidates for other treatment(s). Such approaches have been used to predict freedom from PSAR in patients receiving neoadjuvant ADT and 3D-conformal radiation [3].

A delay in testosterone recovery in PC patients receiving intermittent LHRH-A therapy has been reported elsewhere [36, 37]. Irani et al. reported delayed testosterone recovery in 12 PC patients treated with an LHRH-A for ≥2 years (median 36.9 months, range 24.4 to 64.9 months) [36]. Persistent castrate testosterone levels were noted in six (50%) patients six months after the LHRH-A was stopped. Hall et al. studied LH and testosterone recovery in 14 PC patients receiving an LHRH-A for ≥2 years [37]. Four (29%) of 14 patients had significantly suppressed testosterone levels (<50 ng/dl) after one year, with the median testosterone level in all patients at that time being 110 ng/dl. In that study, no relation was found between the duration of LHRH-A therapy and the time-course of testosterone recovery.

We hypothesize that older PC patients may be more susceptible to prolonged testosterone suppression than younger patients. The median age of patients in the study by Irani et al. was 82 years, which was older than the median patient age of 70 years in the study by Hall et al. and the median patient age of 66 years in our study. We feel that limiting the on-phase IAD duration to <2 years in patients >70 years old should reduce the risk of prolonged testosterone suppression.

It remains unclear whether IAD, as opposed to continuous ADT, will avoid or delay the emergence of AIPC. Labrie et al. treated patients with localized PC using continuous ADT and demonstrated effective disease control as well as a low incidence of AIPC [38]. This pilot study involved 26 untreated clinical stage T1 patients randomized to neoadjuvant ADT followed by radical prostatectomy [39] or external beam radiation therapy [40]. These patients had refused local therapy and remained on continuous ADT. All reached a UD-PSA and continued ADT for a median of 7.1 years (range 2.8-11.8 years). Of 26 patients, one developed a rising PSA after 8.3 years on ADT. In 17 of 26 patients, ADT was stopped after a median duration of 7.3 years; with a median follow-up of 2.4 years, only three patients (18%) developed a rising PSA. Labrie et al. also reported results in another 26 patients with stage T1 disease treated with ADT for a median of 9.9 years. After ADT was stopped, only four patients (15%) have shown a rising PSA after a median follow-up of 1.8 years. In two patients, ADT was restarted when the PSA rose to 6.0 and 7.0 ng/ml, respectively. The PSA dropped to undetectable levels in both patients.

Serum testosterone levels were not reported in the Labrie study. Given the risk of prolonged testosterone suppression discussed earlier with prolonged ADT duration, it is probable that this phenomenon may at least in part explain the high proportion of patients remaining off IAD in the Labrie study. Future IAD trials need to define the optimal on-phase IAD duration that provides a prolonged time off ADT and also permits testosterone recovery within a reasonable time period.

In our clinical practice, continuous ADT is associated with a wide spectrum of androgen deprivation symptoms that diminish quality of life and can be associated with serious medical and surgical problems. Androgens mediate a multitude of functions that include erythropoiesis, bone growth, muscle mass, libido, potency, and cognitive function. Absence or decline in androgen is also associated with secondary weight gain, hyperlipidemia, hypertension, diabetes, dryness of skin, brittleness of nails, and hot flushes. This constellation of signs and symptoms due to ADT varies from patient to patient. It is important to note that some of the more serious side effects of ADT such as anemia and bone resorption can be effectively treated or prevented [41, 42]. Other side-effects such as diminished libido, impotence, cognitive dysfunction, weight gain and muscle loss are being studied [43, 44].

CONCLUSIONS
Hormone-naïve patients who achieve and maintain a UD-PSA for at least one year during ADT may initiate IAD and anticipate a prolonged off-phase duration. Patients with PSAR and/or require ≥4 months to reach a testosterone level ≥150 ng/dl after ADT is stopped may not require a second cycle of IAD for years. Those with low-volume disease requiring ADT in the future appear to have ADPC and respond well to subsequent IAD cycles. Our approach with IAD has been to use the sensitivity of the tumor cell population to ADT to effectively select patients with ADPC, and to optimize apoptosis by prolonged exposure to ADT. Clinical trials are necessary to determine the optimal on-phase duration of IAD to achieve maximal time off ADT without jeopardizing patient survival.

ACKNOWLEDGMENT
Supported by the Freeman Hospitals Foundation, Inc., Grant Number 443.
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