Prostate cancer: finasteride extends PSA doubling time during intermittent hormone therapy

Jennifer A. Locke, PhD, Nicholas Bruchovsky, MD
The Prostate Centre at Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada

LOCKE JA, BRUCHOVSKY N. Prostate cancer: finasteride extends PSA doubling time during intermittent hormone-therapy. The Canadian Journal of Urology. 2010;17(3):5162-5169.

Objectives: *Finasteride has been shown to prolong the time off-treatment in men with prostate cancer during intermittent androgen suppression therapy, but it is not clear whether this results from an increase in prostate-specific antigen (PSA) doubling time or a delay in PSA responsiveness to regained testicular function. In the following study, we distinguish between these two possibilities and consider how the effectiveness of finasteride might be altered if androgens are synthesized within the malignant cell rather than the testis.*
Subjects and methods: *Six patients were followed on intermittent androgen suppression for intervals ranging from 7 to 10 years. The effects of finasteride on the length of the off-treatment period in at least one cycle in each patient were measured with monthly determinations of serum PSA and testosterone and calculation of PSA doubling time using linear regression analysis.*
Results: *Administration of finasteride was associated with a reduction in the rate of increase of serum PSA in the off-treatment period of any given cycle within a sequence of 5. In a total of 15 cycles, finasteride extended PSA doubling time from a mean of 7.7 weeks (n = 11, range 2.3-29.8 weeks) to a mean of 45.1 weeks (n = 6, range 13.8-99.7 weeks). One patient was characterized by an apparent pseudo-resistance to finasteride in the 2nd cycle of treatment and another patient by complete resistance to finasteride in the 4th cycle.*
Conclusions: *Finasteride can be introduced into any cycle of intermittent androgen suppression with the expectation of an extension of PSA doubling time.*

Key Words: prostate cancer, androgens, intermittent androgen suppression, finasteride, castration resistant, androgen independent

Introduction

Intermittent androgen suppression is an acceptable option for the care of patients with recurrent prostate cancer[1,2] as it has been shown to have equivalent efficacy to continuous androgen deprivation therapy with reduced overall side effects and a lower cost burden on the health care system.[3,4] In efforts to further delay disease progression investigators have begun to evaluate the effectiveness of second-line drugs in the off-treatment period of cyclic treatment. For example, it has been reported recently that thalidomide in combination with intermittent androgen suppression resulted in an extension of approximately 6 months in prostate-specific antigen (PSA) defined progression as compared to intermittent therapy alone.[5] Another potential approach to prolong the off-treatment interval is to block the conversion of testosterone to dihydrotestosterone using inhibitors of 5-alpha reductase by agents such as finasteride and dutasteride.[6] Our preliminary clinical experience with finasteride suggested that time off-treatment might be increased if the drug was administered at the time of interruption of androgen withdrawal therapy.[7] In experimental studies based on the LNCaP xenograft

Accepted for publication February 2010

Acknowledgements
This study was made possible by financial support from the Liber Ero Foundation of Vancouver. We thank the staff of the Tumor Marker Laboratory at the British Columbia Cancer Agency for expert biochemical testing, Jonas Abersbach for information technology support and Alla Sekunova for typing and editing the article.

Address correspondence to Dr. Jennifer A. Locke, The Prostate Centre at Vancouver General Hospital, 2660 Oak Street, Vancouver, BC, V6H 3Z6 Canada

model of prostate cancer Eggener et al[8] found that the administration of finasteride during the off-treatment period of cycle 1 therapy resulted in a reduction of tumor growth and a 3- to 5-fold increase in the likelihood of survival at 70 days when compared to the results obtained with continuous androgen deprivation, continuous androgen deprivation and finasteride or with intermittent androgen suppression alone. Using data from a retrospective study of 101 men with advanced prostate cancer treated on an intermittent therapy protocol, Scholz et al[9] reported that finasteride doubled the duration of time off-treatment and did not induce earlier emergence of androgen independent disease after 9 years of follow up. However, results available from the foregoing studies do not indicate whether lengthening of the time off-treatment is related to an increase in PSA doubling time, a delay in the recovery of testicular function or a combination of both factors. Nor do they address the question whether the synthesis of testosterone within prostatic cells[10-12] contributes at any time to alterations in PSA doubling time and also whether finasteride can target both known pathways of dihydrotestosterone formation in the cell equally well, Figure 1. Our present retrospective study examines these points.

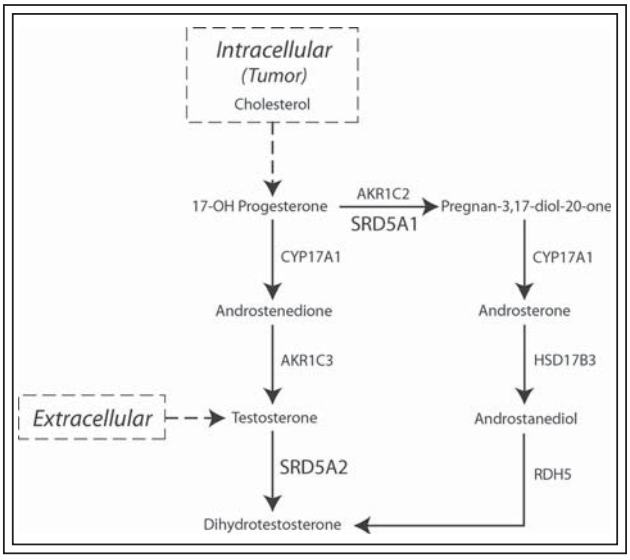

Figure 1. Extracellular and intracellular pathways for the formation of dihydrotestosterone. Intracellular synthesis can occur via two pathways from 17-OH progesterone as depicted. Enzymes in the intracellular synthesis pathways include CYP17A1 (cytochrome P450 17A1), AKR1C2 and AKR1C3 (aldo-keto reductase family members 2 and 3), HSD17B3 (hydroxysteroid dehydrogenase 3), RDH5 (retinol dehydrogenase 5) and SRD5A1 and SRD5A2 (steroid 5-alpha reductases 1 and 2).

Subjects and methods

Patients

Six patients with histologically confirmed adenocarcinoma and rising serum PSA levels after external-beam irradiation of the prostate and/or radical retropubic prostatectomy were chosen as representative cases to address the questions posed in this study. Patients had varying clinical stages and Gleason scores as described in the figure legends.

Measurement of serum PSA and testosterone

Serum PSA and testosterone concentrations were measured as previously reported.[13] Briefly, serum samples were extracted from blood collected from patients in the morning and analyzed using the Abbott AxSYM Total PSA mono/mono assay for PSA concentrations and the DPC Coat-A-Count total testosterone radioimmunoassay method for testosterone concentrations.

Determination of PSA doubling time

PSA doubling time was determined for each cycle by plotting a linear regression line through serial PSA measurements from the closest point of the first increase in serum PSA to the closest point of the first indication of an exponential increase in serum PSA or the last available data point. The doubling time was then calculated from the formula: ln2/slope (m), (m = lnPSA/time) of the regression line[14] where the slope was calculated using the Excel program. Figures depict both the linear slope (m), (m = PSA/time) of the regression line and the corresponding correlation coefficient (r) for each cycle. All values are reported in the unit of weeks.

Ethical review

All patients provided written informed consent in accordance with institutional guidelines.

Results

Effect of addition of off-treatment finasteride on PSA doubling time

An effect of finasteride was observed in up to five consecutive cycles of intermittent androgen suppression in patients exhibiting biochemically recurrent disease. The change in PSA doubling time in the cycle 1 off-treatment period is depicted in Figure 2a in a patient aged 52 years who relapsed after surgery and radiotherapy. Without finasteride, the increase in serum PSA was characterized by a slope of m = 0.0316 µg/L/week (r = 0.9854). With the administration of finasteride

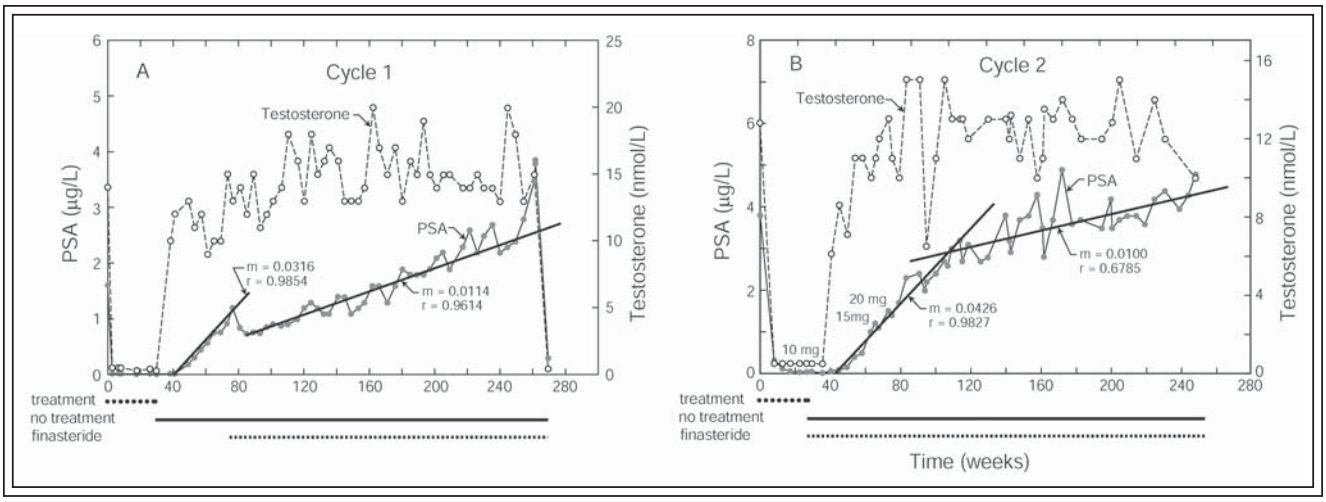

Figure 2. Effect of finasteride on cycle 1 and cycle 2 off-treatment period PSA doubling time. Six years after radical retropubic prostatectomy and radical radiotherapy this 52-year-old patient was started on a regime of intermittent androgen suppression. A combination of cyproterone acetate and leuprolide acetate was used as treatment. At the time of diagnosis this patient displayed a clinical stage B2 moderately differentiated adenocarcinoma with a Gleason score of 7 and a PSA of 15 µg/L. **a)** After interruption of androgen withdrawal therapy in cycle 1, the administration of finasteride (10 mg/day) was delayed until the 77 week time point when the serum testosterone concentration was in the normal range. This had the effect of changing the initial slope m = 0.0316 to m = 0.0114 µg/L/week equivalent to a lengthening of the PSA doubling time from 7.2 weeks to 91.2 weeks. **b)** After interruption of androgen withdrawal therapy in cycle 2, the administration of finasteride was started without delay at a dose of 10 mg/day which had no effect on the initial slope; the dose was then increased to 15 mg/day and 20 mg/day at intervals as shown. After administration of the highest dose, the initial slope changed from m = 0.04726 µg/L/week to, m = 0.0100 µg/L/week equivalent to lengthening of the PSA doubling time from 12.9 weeks to 244.1 weeks. Slope (m) of the regression line was used to calculate doubling time as described under Subjects and methods. Correlation coefficient (r) is also shown.

starting at 76 weeks, the slope was reduced by more than one half to m = 0.0114 µg/L/week (r = 0.9614); thus finasteride resulted in a lengthening of PSA doubling time from 7.2 weeks to 91.2 weeks.

The effect of finasteride in cycle 2 is depicted in Figure 3a in a patient aged 75 years in biochemical relapse after radiation therapy. The PSA doubling time in cycle 2 initially was characterized by a slope of m = 0.1850 µg/L/week (r = 0.9788) that was almost 3-fold greater than the initial slope in cycle 1 i.e. m = 0.065 µg/L/week (r = 0.9876). For this reason finasteride was introduced at approximately 260 weeks resulting in a 5-fold decrease in the slope to m = 0.0371 µg/L/week (r = 0.9033). This change was associated with a lengthening of PSA doubling time from 6.0 weeks before the introduction of finasteride to 99.7 weeks after.

The effects of finasteride in cycles 2 and 3 are depicted in Figure 3b in a patient aged 59 years with PSA recurrent disease after radiotherapy. The PSA doubling time in cycle 1 was characterized by a slope of m = 0.9848 µg/L/week (r = 0.9739) that was 3-fold greater than the slope in cycle 2, m = 0.3119 µg/L/week (r = 0.9895) and almost six times greater than the slope in cycle 3, m = 0.1755 (r = 0.9648). This resulted in an extension of PSA doubling time from 5.8 weeks in cycle 1 to 13.8 weeks and 28.2 weeks in cycles 2 and 3, respectively. Unlike the examples in Figure 2a and Figure 3a, in both cycles 2 and 3 in Figure 3b, finasteride was introduced in the off-treatment period at the time of interruption of androgen suppression therapy rather than at the time when a normal level of serum testosterone had been achieved. Also, note the long 30 week delay in recovery of serum testosterone in cycle 3 in the interval between 230 weeks and 260 weeks contributing to the prolongation of the total time off-treatment.

The effect of finasteride on cycle 4 is depicted in Figure 3c in a patient aged 63 years in biochemical relapse after surgery and radiation therapy. The PSA doubling time in the first three cycles was characterized by slopes of m = 1.000 µg/L/week (r = 0.9974), m = 0.9950 µg/L/week (r = 0.9778), m = 1.3714 µg/L/week (r = 0.9697) respectively, yielding a mean value of

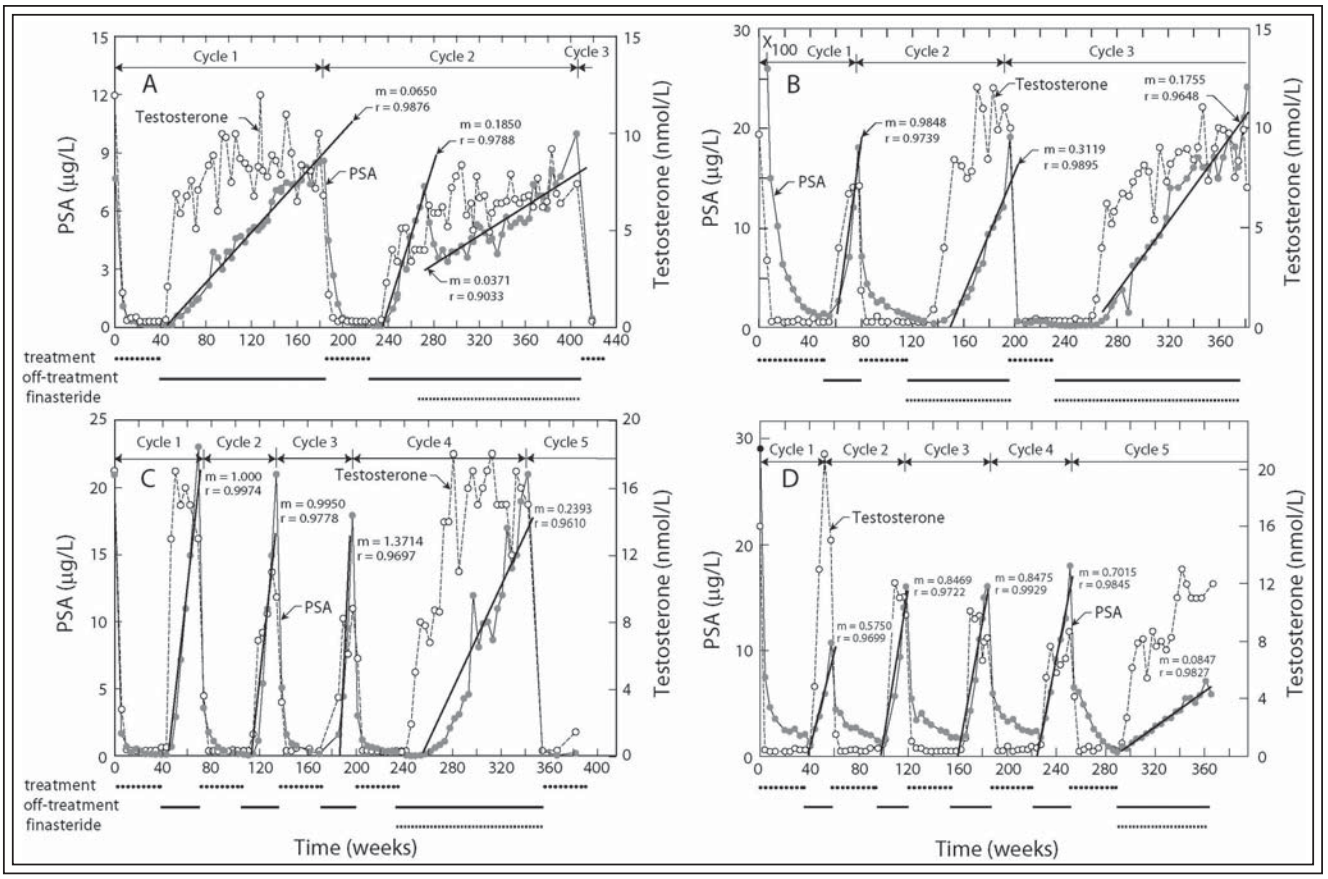

Figure 3. a) Effect of finasteride on cycle 2 off-treatment PSA doubling time. Four years after radical radiotherapy this 75-year-old patient was started on a regime of intermittent androgen suppression based on a combination of cyproterone acetate and leuprolide acetate. At the time of diagnosis the patient displayed a clinical stage C moderately differentiated adenocarcinoma with a Gleason score of 7. In the cycle 1 off-treatment period with no finasteride, the PSA doubling time was characterized by a slope m = 0.065 µg/L/week. In the initial part of the cycle 2 off-treatment period, the PSA doubling time was shorter being characterized by a slope m = 0.1850 µg/L/week. Finasteride was introduced at week 260 and resulted in a 4.5 fold decrease in the slope to m = 0.0371 µg/L/week, equivalent to a lengthening of the PSA doubling time from 6.0 weeks before finasteride to 99.7 weeks after. Values for slope (m) and correlation coefficient (r) are shown for each off-treatment period. **b)** Effect of finasteride on cycle 2 and cycle 3 off-treatment PSA doubling times. This 59-year-old patient was started on a regime of intermittent androgen suppression after relapse from radical prostatectomy for clinical stage C disease at diagnosis. A combination of cyproterone acetate and leuprolide acetate was used as treatment. Cycle 1 was completed without addition of finasteride. In cycle 2 and cycle 3, the patient was started on finasteride at a dose of 10 mg/day at the beginning of the off-treatment period in each cycle. Values for slope (m) and correlation coefficient (r) are shown for each off-treatment period. **c)** Effect of finasteride on cycle 4 off-treatment PSA doubling time. Two years after radical radiotherapy this 63-year-old patient was started on a regime of intermittent androgen suppression. A combination of cyproterone acetate and leuprolide acetate was used as treatment. At the time of diagnosis this patient displayed a clinical stage B2 poorly differentiated adenocarcinoma with a Gleason score of 8 and a PSA of 48 µg/L. The first three cycles were completed without finasteride. At the beginning of the cycle 4 off-treatment period the patient was started on finasteride at a dose of 10 mg/day. Values for slope (m) and correlation coefficient (r) are shown for each off-treatment period. **d)** Effect of finasteride on cycle 5 off-treatment PSA doubling time. Three years after radical radiotherapy this 73-year-old patient was started on a regime of intermittent androgen suppression using a combination of cyproterone acetate and leuprolide acetate. At the time of diagnosis this patient displayed a clinical stage C moderately differentiated adenocarcinoma with a Gleason score of 5 and a PSA of 24 µg/L. The first four cycles were completed without finasteride. At the beginning of the cycle 5 off-treatment period, the patient was started on finasteride at a dose of 10 mg/day. Values for slope (m) and correlation coefficient (r) are shown for each off-treatment period.

1.1221 µg/L/week. This represents a 5-fold faster doubling time relative to the slope in cycle 4 of m = 0.2393 µg/L/week (r = 0.9610) resulting from the administration of finasteride. The PSA doubling time increased from a mean of 3.5 weeks in cycles 1-3 to 13.9 weeks in cycle 4. Note that in successive cycles, the peak level of serum testosterone decreased from 17 nmol/L in cycle 1 to 11 nmol/L in cycle 2 and 9 nmol/L in cycle 3. With the addition of finasteride in cycle 4, the peak level of serum testosterone recovered to 18 nmol/L.

The effect of finasteride on cycle 5 is shown in Figure 3d in a patient aged 73 years with PSA recurrent disease after radiotherapy. The PSA doubling time in the first four cycles was characterized by slopes of m = 0.5750 µg/L/week (r = 0.9699), m = 0.8469 µg/L/week (r = 0.9722), m = 0.8475 µg/L/week (r = 0.9929), m = 0.7015 µg/L/week (r = 0.9845) respectively, yielding a mean value of 0.7427 µg/L/week. The latter represents an approximate 9-fold faster PSA doubling time relative to the slope in cycle 5 of m = 0.0847 µg/L/week (r = 0.9827) achieved with the administration of finasteride. This resulted in a prolongation of PSA doubling time from a mean of 6.4 weeks in cycles 1-4 to 23.6 weeks in cycle 5. Furthermore, the results in Figure 3d show a decrease in the peak level of serum testosterone in each of successive cycle i.e. 21 nmol/L, 12 nmol/L, 10 nmol/L, 8.6 nmol/L respectively for cycles 1-4, partly restored in cycle 5 to a level of 13 nmol/L by the addition of the off-therapy finasteride.

From the foregoing results, it is evident that finasteride decreased the PSA velocity and extended the PSA doubling time in all patients regardless of cycle evaluated. The mean PSA doubling time without finasteride was 7.7 weeks (n = 11, range 2.3-29.8 weeks) and this changed to a mean of 45.1 weeks (n = 6, range 13.8-99.7 weeks) with the addition of finasteride. Thus, the effect of finasteride on prolonging the PSA doubling time was approximately 6-fold.

Resistance to finasteride

The PSA doubling time may not be responsive to finasteride in all situations. Our observations encompass outcomes that suggest the possibilities of partial and complete insensitivity to the drug. The results depicted in Figure 2a show a pronounced lengthening of PSA doubling time related to the administration of finasteride. However, when the same dose of 10 mg was prescribed at the time of interruption of androgen withdrawal therapy in cycle 2, Figure 2b, the expected slope of m = 0.0114 µg/L/week (r = 0.9614) attained in cycle 1, Figure 2a, failed to materialize. Instead the initial PSA doubling time was characterized by a slope m = 0.0426 µg/L/week (r = 0.9827) equivalent to a marked shortening of PSA doubling time from 91.2 weeks in cycle 1 to 12.9 weeks in cycle 2. However, with escalating doses of finasteride to 20 mg daily the slope was altered to m = 0.0100 µg/L/week (r = 0.6785) representing a protraction of the PSA doubling time from 12.9 weeks to 244.1 weeks. This result suggests that the cancer that was apparently unresponsive to 10 mg and 15 mg of finasteride daily later became responsive to finasteride at the higher dose of 20 mg; subsequently, this was reduced to a maintenance dose of 10 mg daily with no deviation in slope. The changed PSA doubling time with the 20 mg dose in cycle 2 (244.1 weeks) was somewhat similar to the PSA doubling time observed in cycle 1 with the 10 mg dose (91.2 weeks) suggesting that the kinetics of the cancer at the higher dose of finasteride reverted to the original phenotype. The reason for this observed "pseudo-resistance" remains to be determined.

A more complete form of resistance to finasteride, illustrated in Figure 4, was observed in a patient aged 69 years with PSA recurrent disease after radiotherapy. The first three cycles were characterized by slopes of

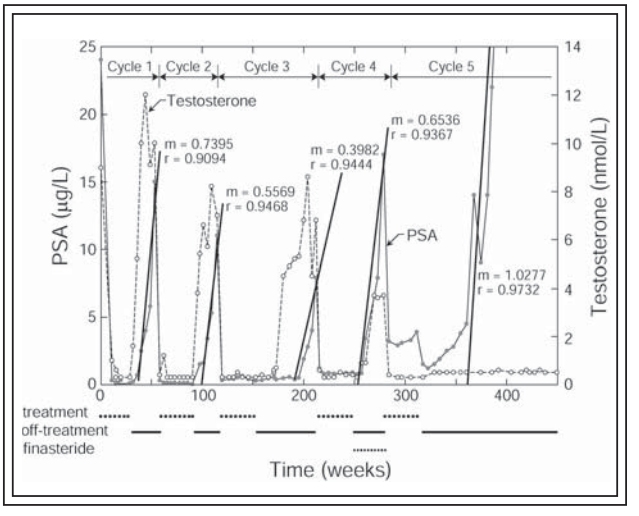

Figure 4. Five cycles of intermittent androgen suppression with finasteride insensitivity. One year after radical prostatectomy this 69-year-old patient was started on a regime of intermittent androgen suppression. At the time of diagnosis this patient displayed a clinical stage C moderately differentiated adenocarcinoma with a Gleason score of 5 and a PSA of 33 µg/L. The first three cycles were completed without finasteride. At the beginning of the cycle 4 off-treatment period, the patient was started on finasteride at a dose of 10 mg/day with no effect on slope. Values for slope (m) and correlation coefficient (r) are shown for each off-treatment period.

m = 0.7395 (r = 0.9094) for cycle 1, m = 0.5569 (r = 0.9468) for cycle 2 and m = 0.3982 (r = 0.9444) for cycle 3 consistent with a slight prolongation of the PSA doubling time as the cycle number increased. However, when finasteride was administered, the PSA doubling time, as indicated by a slope of m = 0.6536 (r = 0.9367) became shorter and thus proved ineffective in contrast to the results in Figures 2, 3a-d. Although resistance to finasteride was suggested by this lack of response, the tumor itself was not androgen independent owing to the observed response to androgen withdrawal therapy at the start of cycle 5. Resistance to treatment was again suggested by the plateauing of serum PSA between 280 and 310 weeks. A change in anti-androgen from bicalutamide to nilutamide at the latter time-point resulted in a drop in serum PSA despite the fact that serum testosterone was at a castrate level. The response was short-lived and the level of serum PSA then increased with a much shorter doubling time characterized by a slope of m = 1.0277 (r = 0.9732) without any change in the level of serum testosterone. It appears that progression to androgen independence took place in cycle 5 over a relatively short period of time. The rapid change to refractory disease might be accounted for by a switch of the dependence of tumor growth from the extracellular to the intracellular synthesis of dihydrotestosterone as shown in Figure 1, although other explanations such as ligand-independent activation of the androgen receptor cannot be ruled out.[11,15]

Discussion

Our study focuses on a small number of men with recurrent prostate cancer undergoing cyclic androgen withdrawal therapy who were followed with monthly determinations of PSA and testosterone for up to 10 years. This serial database, unusual for its extensive detail, afforded us the opportunity to estimate repeated PSA doubling times with considerable accuracy. Previously Scholz et al[9] showed that the administration of finasteride as maintenance therapy after androgen withdrawal therapy increases the time to PSA defined progression, but their study did not encompass estimation of specific effects on PSA doubling time. Our results are consistent with their findings and further demonstrate that the effect of finasteride on increasing time off-treatment results from the prolongation of PSA doubling time, approximately 6 fold in our study, independent of any delay in the recovery of testicular function that adds to the total off-treatment interval. In view of the ability of finasteride to bring about a lengthening of PSA doubling time, even in later cycles, our observations also imply that shortening of successive cycles[1,2,13] is not a specific sign of impending androgen resistance. Another aspect of our study arises from the data compiled on the changes in levels of serum testosterone versus cycle number, a relationship that has not received attention previously in any detail. The results in Figures 3c, d and 4 show a decline in the peak concentration of serum testosterone as the number of cycles increases, a trend that is reversed by finasteride in the cases presented in Figures 3b-d and 4. This attests to the effectiveness of finasteride in reducing the conversion of testosterone to dihydrotestosterone under clinical conditions.

We and others have previously demonstrated that prostatic tissue, either normal or malignant, is capable of synthesizing dihydrotestosterone from cholesterol and adrenal precursors.[10-12] As suggested by the data in Figure 4 (cycle 5) a cancer may progress in the presence of castrate levels of serum testosterone ostensibly because of an emerging reliance on *de novo* synthesis of dihydrotestosterone required for the activation of androgen receptor. In this case the disease appeared to be characterized by a form of complete resistance to finasteride and it was of interest that there was no compensatory increase in the peak level of testosterone during the period of finasteride administration. We infer that in the absence of any impediment to the formation of dihydrotestosterone, no effect on tumor growth would be expected. With continued intracellular production of dihydrotestosterone, the castrate level of serum testosterone would be misleading as to the source of active androgen.

The apparent pseudo-resistance demonstrated in Figure 2b might be explained by the inhibition of 5-alpha reductase type 2, Figure 1, SRD5A2 (characterized by a relatively low inhibitor concentration, IC_{50} = 5.2 ± 0.26 nM[16]) initially with a small dose of finasteride. Conceivably this block could result in a shift in the formation of dihydrotestosterone to the alternative synthesis pathway mediated by 5-alpha reductase type 1, Figure 1, SRD5A1 (characterized by a higher IC_{50} = 23 ± 0.23 nM[16]). In response to a larger dose of finasteride, inhibition of SRD5A1 would then take place and result in a reduced intracellular concentration of dihydrotestosterone. In support of this hypothesis Azzolina et al have previously demonstrated finasteride to reversibly inhibit SRD5A1, although at 100-fold higher doses than that observed for SRD5A2 inhibition.[17]

Another explanation for pseudo-resistance to finasteride could be related to the timing of finasteride

treatment. In cycle 1, Figure 2a, finasteride was introduced after serum testosterone peaked in a normal range while in cycle 2, Figure 2b, finasteride was introduced immediately after androgen withdrawal therapy was interrupted. In theory the administration of finasteride could be delayed until the concentration of serum testosterone is in the normal range; however, since normalization of serum testosterone becomes less predictable as the number of cycles increases,[13] it is more practical to start therapy with finasteride at the time of interruption of androgen withdrawal therapy. The latter practice was employed routinely after the erratic pattern of recovery of serum testosterone became apparent.

We have previously observed that the induction of 5-alpha reductases, both SRD5A1 and SRD5A2, is a requirement preceding *de novo* androgen synthesis.[15] As these enzymes are likely androgen-regulated target genes,[18,19] we speculate that in order for finasteride to be effective, the induction of the reductases must take place beforehand in response to an increasing concentration of testosterone. This would account for the fact that finasteride was immediately effective in cycle 1, Figure 2a, but not in cycle 2, Figure 2b.

Our clinical experience with finasteride indicates that apparent anomalies can arise when the drug is used to prolong the off-treatment interval during the practice of intermittent androgen suppression for prostate cancer. Circumstances that suggest pseudo–resistance or complete resistance to 5-alpha reductase blockade may arise and complicate the interpretation of the results of therapy. Mostaghel et al recently demonstrated that finasteride and dutasteride do indeed reduce the overall incidence of prostate cancer through the reduction in tissue dihydrotestosterone production; however, the authors also note that patients are differentially sensitive to SRD5A1/2 inhibition.[20] Undoubtedly more insight into these mechanisms will be gained as the uses of finasteride and dutasteride[19] are explored further to improve outcomes with cyclic androgen suppression.

As the activation of the androgen receptor remains important in disease progression it would be logical to focus attention on the preservation of receptor function so that a tumor remains androgen dependent and subject to control through regulation of 5-alpha reductase activity. In developing new strategies to delay the emergence of hormone refractory disease, further clinical evaluation of the use of 5-alpha reductase inhibitors in combination with intermittent androgen suppression should prove worthwhile. □

References

1. Bruchovsky N, Klotz L, Crook J, Malone S, Ludgate C, Morris WJ, Gleave ME, Goldenberg SL. Final results of the Canadian prospective phase II trial of intermittent androgen suppression for men in biochemical recurrence after radiotherapy for locally advanced prostate cancer: clinical parameters. *Cancer* 2006;107(2):389-395.
2. Bruchovsky N, Klotz L, Crook J, Phillips N, Abersbach J, Goldenberg SL. Quality of life, morbidity, and mortality results of a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen relapse after radiation therapy for locally advanced prostate cancer. *Clin Genitourin Cancer* 2008;6(1):46-52.
3. Tunn U. The current status of intermittent androgen deprivation (IAD) therapy for prostate cancer: putting IAD under the spotlight. *BJU Int* 2007;99(Suppl 1):19-22.
4. Seruga B, Tannock IF. Intermittent androgen blockade should be regarded as standard therapy in prostate cancer. *Nature Clin Pract Oncol* 2008;5(10):574-576.
5. Figg WD, Hussain MH, Gulley JL, Arien PM, Aragon-Ching JB, Petrylak DP, Higano CS, Steinberg SM, Chatta GS, Parnes H, Wright JJ, Sartor O, Dahut WL. A double-blind randomized crossover study of oral thalidomide versus placebo for androgen dependent prostate cancer treated with intermittent androgen ablation. *J Urol* 2009;181(3):1104-1113.
6. Andriole G, Bruchovsky N, Chung LW, Matsumoto AM, Rittmaster R, Roehrborn C, Russell D, Tindall D. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J Urol* 2004;172(4 Pt 1):1399-1403.
7. Bruchovsky N, Klotz LH, Sadar M, Crook JM, Hoffart D, Godwin L, Warkentin M, Gleave ME, Goldenberg SL. Intermittent androgen suppression for prostate cancer: Canadian Prospective Trial and related observations. *Mol Urol* 2000;4(3):191-199.
8. Eggener SE, Stern JA, Jain PM, Oram S, Ai J, Cai X, Roehl KA, Wang Z. Enhancement of intermittent androgen ablation by "off-cycle" maintenance with finasteride in LNCaP prostate cancer xenograft model. *Prostate* 2006;66(5):495-502.
9. Scholz MC, Jennrich RI, Strum SB, Johnson HJ, Guess BW, Lam RY. Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period. *J Urol* 2006;175(5):1673-1678.
10. Bruchovsky N, Lesser B, Van Doorn E, Craven S. Hormonal effects on cell proliferation in rat prostate. *Vitam Horm* 1975;33:61-102.
11. Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, Ettinger SL, Gleave ME, Nelson CC. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res* 2008;68(15): 6407-6415.
12. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, True LD, Nelson PS. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008;68(11):4447-4454.
13. Bruchovsky N, Klotz L, Crook J, Goldenberg SL. Locally advanced prostate cancer--biochemical results from a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen recurrence after radiotherapy. *Cancer* 2007;109(5):858-867.
14. Svatek RS, Shulman M, Choudhary PK, Benaim E. Critical analysis of prostate-specific antigen doubling time calculation methodology. *Cancer* 2006;106(5):1047-1053.
15. Sadar MD, Hussain M, Bruchovsky N. Prostate cancer: molecular biology of early progression to androgen independence. *Endocr Relat Cancer* 1999;6(4):487-502.

16. Locke JA, Nelson CC, Adomat HH, Hendy SC, Gleave ME, Guns ES. Steroidogenesis inhibitors alter but do not eliminate androgen synthesis mechanisms during progression to castration-resistance in LNCaP prostate xenografts. *J Steroid Biochem Mol Biol* 2009;115(3-5):126-136.
17. Azzolina B, Ellsworth K, Andersson S, Geissler W, Bull HG, Harris GS. Inhibition of rat alpha-reductases by finasteride: evidence for isozyme differences in the mechanism of inhibition. *J Steroid Biochem Mol Biol* 1997;61(1-2):55-64.
18. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, Febbo PG, Balk SP. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res* 2006;66(5):2815-2825.
19. Tindall DJ, Rittmaster RS. The rationale for inhibiting 5alpha-reductase isoenzymes in the prevention and treatment of prostate cancer. *J Urol* 2008;179(4):1235-1242.
20. Mostaghel EA, Geng L, Holcomb I, Coleman IM, Lucas J, True LD, Nelson PS. Variability in the androgen response of prostate epithelium to 5{alpha}-reductase inhibition: implications for prostate cancer chemoprevention. *Cancer Res*.2010;70(4): 1286-1295.

EDITORIAL COMMENT

The idea of intermittent hormonal therapy for recurrent and/or metastatic prostate cancer is appealing due to its presumed benefits of decreased cost, better quality of life and prolonged androgen sensitivity, although the latter was not substantially proven so far.

Recently, the concept of further delay of disease progression and prolongation of the off-treatment period (OTP) by additional pharmacological intervention has been introduced with a certain degree of effectiveness as has been suggested by a retrospective study (Reference 9 in the manuscript). Evidence suggested that finasteride doubles the duration of time off-hormonal therapy and AIPC was not increased by finasteride after almost 9 years of observation.[1]

Although, the kinetics of serum testosterone normalization after limited hormonal manipulation appears to be important in determination of OTP, entire process appears to be more complicated with the reported evidence that castrate resistant prostate cancer contain sufficient levels of testosterone and dihydrotestosterone (DHT) for AR transactivation as well as express all necessary enzymes for de novo DHT synthesis, and capable of intratumoral conversion of precursors to DHT alongside the usage of progesterone to synthesize DHT via steroidogenic pathways.[2]

Thus, interference with intracellular conversion of T to DHT may provide additional interim control of disease, as indicated by the results of the current study. Treatment by finasteride resulted in a decrease of PSA velocity and extended the PSA doubling time in all patients regardless of cycle evaluated. The mean PSA doubling time without finasteride was 7.7 weeks which was increased to a mean of 45.1 weeks with the addition of finasteride, which translates to a 6-fold increase. Yet the underlying molecular mechanisms are still questionable and actual role of 5-alpha reductase iso-enzymes (type 1 and 2) remains to be identified. A recent study indicated increased levels of 5 alpha-reductase type 1 and 2 in localized high grade prostate cancer compared to low grade tumors,[3] indicating a grade dependent differential expression of these iso-enzymes. Levels of 5 alpha-reductase type 1 were also higher in benign tissue adjacent to cancer than in benign prostatic hyperplasia. These results raise the possibility that increased 5 alpha-reductase type 1 in localized high grade cancers may contribute to the decreased effectiveness of the type 2 selective inhibitors, which may also in part explain the so called "pseudo-resistance" observed in some cases in the current study. It is still questionable whether dual inhibitors like dutasteride would be more effective in terms of achieving a longer OTP in this setting. Hopefully, optimal selection and timing of agents will be clarified by further investigations.

References

1. Scholz MC, Jennrich RI, Strum SB, Johnson HJ, Guess BW, Lam RY. Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period. *J Urol* 2006;175(5):1673-1678.
2. Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, Ettinger SL, Gleave ME, Nelson CC. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res* 2008;68(15): 6407-6415.
3. Thomas LN, Douglas RC, Lazier CB, Gupta R, Norman RW, Murphy PR, Rittmaster RS, Too CK. Levels of 5alpha-reductase type 1 and type 2 are increased in localized high grade compared to low grade prostate cancer. *J Urol* 2008;179(1):147-151.

Levent Türkeri, MD
Department of Urology
Marmara University School of Medicine
Istanbul, Turkey