Intermittent Use of Testosterone Inactivating Pharmaceuticals Using Finasteride Prolongs the Time Off Period

Mark C. Scholz,* Robert I. Jennrich, Stephen B. Strum, Henry J. Johnson, Brad W. Guess and Richard Y. Lam

From the Prostate Oncology Specialists, Marina del Rey and Department of Statistics, University of California-Los Angeles, Los Angeles, California

Purpose: Men with prostate cancer treated intermittently with TIP benefit from improved quality of life when TOP with recovered testosterone is prolonged. We examined factors influencing the duration of TOP.

Materials and Methods: We retrospectively reviewed the charts of 101 men treated with intermittent TIP in a 9-year period. Men with positive bone scan, men in whom a PSA nadir of less than 0.1 ng/ml on TIP failed to be achieved and maintained and men in whom testosterone failed to recover to greater than 150 ng/dl during the first 12 months of TOP were excluded. Potential factors predicting prolonged TOP or accelerated time to AIPC were studied with Cox regression analysis.

Results: Patient characteristics were clinical stage T1c-T2a in 51 and T2b-T3b in 11, PSA relapse in 29, and T3c, D0 or D1 in 10. Median PSA was 7.6 ng/ml, Gleason score was 3 + 4 = 7 and TIP duration was 15.8 months. The 60 group 1 patients received finasteride and the 41 in group 2 received no finasteride. Median TOP in groups 1 and 2 was 31 and 15 months, respectively, using Kaplan-Meier analysis. Cox regression analysis indicated that longer TIP, finasteride and increased age predicted longer TOP. A slow PSA decrease while on TIP, higher baseline PSA and increased Gleason score predicted shorter TOP. Cox regression analysis indicated that only higher clinical stage but not finasteride predicted the earlier onset of AIPC.

Conclusions: Finasteride doubles the duration of TOP. AIPC was not increased by finasteride after almost 9 years of observation.

Key Words: prostate, prostatic neoplasms, finasteride androgen antagonists

There has been increasing TIP use as initial therapy for localized prostate cancer as well as for recurrence after surgery or radiation. Historically physicians have been reluctant to administer early TIP because the undesirable side effects become more pronounced with the prolonged exposure times associated with continuous TIP in early stage disease.

The side effects of long-term testosterone inactivation are not trivial and they may include fatigue, weakness, sarcopenia, hot flashes, loss of libido, impotence, loss of bone mineral density, weight gain, anemia and others, of which all are directly related to the paucity of testosterone. A number of maneuvers, such as resistance training, diet and various pharmaceutical agents, are available to decrease the undesirable effects of testosterone loss. Although these interventions improve patient status, most often the amelioration is just partial. Only the restoration of normal testosterone restores patient quality of life to pre-deprivation levels.

A way to decrease the side effects of long-term testosterone deprivation is to permit periodic treatment holidays, stopping TIP and allowing testosterone to normalize. The intermittent TIP philosophy postulates that the anticancer effect of TIP administered in an on and off schedule is equivalent or even superior to TIP administered continuously.[1] To our knowledge there is no long-term published study proving the equivalence of these 2 approaches. However, preliminary results in 2 small, randomized studies show no evidence of an accelerated time to androgen independence with either approach.[2,3] A randomized study of 550 patients showed no difference in outcome between continuous and intermittent therapy.

Some conventions have arisen around how intermittent TIP is administered (fig. 1). In all studies PSA is used as an indicator to signal when TIP should be stopped. Hence, TIP is discontinued when PSA decreases to or below some predetermined threshold, although in some cases TIP is continued for a specified period after that threshold is attained. During the intermittent or off phase of TIP testosterone recovers and PSA increases. TIP is restarted for a second time when PSA achieves another arbitrarily predetermined threshold, thus, signaling the end of the first cycle.

Accepting that restored testosterone is synonymous with improved quality of life and intermittent exposure to testosterone does not accelerate the development of AIPC, one can logically conclude that prolonged TOP would result in improved quality of life. Since quality of life is inextricably associated with the amount of time that men can spend enjoying recovered testosterone, we believed that it would be useful to identify factors resulting in more extended TOP.

Several studies suggest that finasteride has activity against prostate cancer and, therefore, it is a likely candidate for prolonging TOP. In men with PSA relapse after

Submitted for publication June 17, 2005.

Presented at annual meeting of American Urological Association, Dallas, Texas, May 1-6, 1999.

* Correspondence: 4676 Admiralty Way, No. 101, Marina del Rey, California 90292 (telephone: 310-827-7707; FAX: 310-574-4002; e-mail: Mark@prostateoncology.com).

DOI:10.1016/S0022-5347(05)00975-4

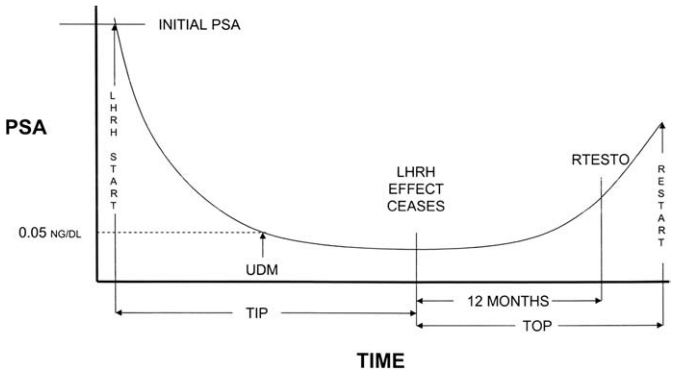

FIG. 1. One cycle of intermittent TIP

radical prostatectomy, finasteride causes a 1 to 2-year delay in PSA increase.[4] Finasteride enhances TIP therapy for prostate cancer,[5] acts as a diagnostic maneuver to detect underlying prostate cancer[6] and results in deeper PSA nadirs compared to antiandrogen treatment alone.[7] Finasteride administered in a large, randomized prevention study was shown to decrease the incidence of new prostate cancers by 25%.[8] These wide-ranging effects are believed to result from finasteride selectively blocking the enzymatic conversion of testosterone into more potent dihydrotestosterone.

A concern raised about the finasteride prevention study was a 1% increased incidence of higher grade tumors in finasteride treated men compared to those on placebo. Commentary on this finding has been conflicting.[9] The validity of using a pathological end point such as Gleason score in the setting of a hormonally active agent such as finasteride has been challenged because finasteride has been reported to change the histological appearance of malignant cells.[10] Others countered that Gleason scores in patients on finasteride are clinically relevant and reliable.[11] A plausible explanation for the slightly higher incidence of high grade disease is that tumors of similar size would be expected to be found more frequently in smaller (finasteride treated) glands since biopsy of a smaller gland increases the percent of gland volume sampled per core. This line of reasoning concludes that finasteride is not causing high grade disease, but rather helping to reveal it.[12] An artifactual rather than biological etiology is also suggested by the reported absence of any trend toward an increasing incidence of higher grade disease as the study progressed, as might be expected if extended exposure to finasteride causes malignant dedifferentiation.[13]

Using PSA as the end point for the termination of TOP in men with a component of benign prostatic hypertrophy is problematic since finasteride decreases prostate gland generated PSA by 50%. However, studies show that finasteride does not disguise the underlying presence of prostate cancer.[14] Since the effect of finasteride on PSA generated from benign prostatic hypertrophy could potentially bias TOP, allowance was made in the study by using a PSA threshold for ending TOP that was 50% lower in men treated with finasteride (2.5 instead of 5.0 ng/ml).

PATIENTS AND METHODS

Patient Selection and Treatment

Charts at an oncology practice specializing in prostate cancer were reviewed for study eligibility. Criteria for inclusion were 1) biopsy proven prostate cancer, 2) negative bone scan, 3) TIP induction with an LHRH agonist combined with an antiandrogen, 4) hormone sensitive disease, as proved by achieving and maintaining PSA less than 0.1 ng/ml during TIP induction,[15] 5) a minimum of 5 years of followup after the initiation of TIP, 6) testosterone recovery greater than 150 ng/dl within 12 months after stopping TIP, and 7) sufficient clinical and laboratory data available for review.

Study Definitions

Patient grouping. Group 1 included 60 men receiving 5 mg finasteride once daily during TOP. Group 2 included 41 men who did not receive finasteride. We assessed age at the start of TIP and IPSA as well as BTESTO. Clinical stage and Gleason score were each segregated into 4 categories (table 1). Gleason score was assigned by internationally recognized pathologists with expertise in prostate cancer. The 2 men meeting criteria to be in the PSA relapse group, or the stage T3c, D0 or D1 group were placed in the latter. UDM was defined as the interval from TIP initiation until PSA decreased below the lower limit of the PSA assay. If, as was usually the case, the assay could measure below 0.1 ng/ml, UDM occurred when PSA decreased to less than 0.05 ng/ml. TIP was defined as the time in months, starting with the first injection of an LHRH agonist and lasting 1 or 3 months after the last LHRH agonist was administered, depending on the dose of the last injection. Antiandrogen was administered concomitantly with 250 mg flutamide orally every 8 hours or 50 mg bicalutamide orally daily. RTESTO was defined as testosterone 12 months after TIP ended. TOP was considered to start at the end of TIP and last until PSA became 2.5 ng/ml in group 1 or 5.0 ng/ml in group 2. TOP was also considered to have ended if any palpable disease could be detected on digital rectal examination or if TIP was restarted for any other reason, such as biopsy or ultrasound findings. AIPC was defined as failure to attain an undetectable PSA of less than 0.1 ng/ml with the reinstitution of TIP, while testosterone remained less than 50 ng/dl. Time of onset of AIPC was the date of the lowest PSA above 0.1 ng/ml (the PSA nadir) in a sequence of nondecreasing PSA levels above 0.1 ng/ml. Time to AIPC onset was measured

TABLE 1. *Stage, Gleason score and long-term outcome in 101 patients*

	No. Group 1	No. Group 2
Clinical stage:		
T1c or T2a	32	19
T2b–T3b	8	3
PSA relapse	15	14
T3C, D0 or D1	5	5
Gleason score:		
Less than 7	29	19
3 + 4 = 7	14	6
4 + 3 = 7	10	7
More than 7	7	9
Long-term TOP outcome:		
Still on cycle 1	9	2
Started cycle 2	31	36
Started cycle 3	12	19
Started cycle 4	3	6
Started cycle 5	0	1
Delayed local treatment	7	10
AIPC	8	12
Death:		
Prostate Ca	1	4
Other cause	10	7