SEATTLE PROSTATE INSTITUTE

PCa Commentary

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Contents

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DIAGNOSTICS

Interaction Of Finasteride (Proscar) And Psa: A Potential Problem In Diagnosis It has been well documented that when 5 mg of finasteride is used for the treatment of BPH the total PSA falls by 50%. Less clear is the interpretation of the change in the percent free PSA (%fPSA) in instances wherein patients are under treatment with finasteride. A clinical example serves to point up important issues associated with this not uncommon diagnostic challenge.

Consider the following: A 70+ year old man's total PSA (tPSA) results on 5/1996 were 3.6 ng/ml, %fPSA 18%; on 7/2000 the tPSA was 4.2 ng/ml, %fPSA 25%; on 10/2002 tPSA 6.7 ng/ml, %fPSA 21%. Because of urinary symptoms from an enlarged gland, he was prescribed finasteride 5 mg. On 5/2003 the tPSA was 3.9 ng.ml, a 42% reduction, and the %fPSA was 7.9%. What to think?

The next reasonable step would be to recheck the results. The national press gave widespread coverage to the recent JAMA article, "Variation of Serum Prostate-Specific Antigen Levels", which essentially reframed the carpenters' old adage - "Measure twice, cut once", suggesting that a physician considering a biopsy on the basis of a upward change in PSA should recheck the PSA result. With reference to the example above, the values were rechecked yielding the following results: tPSA was 2.5 ng/ml with %fPSA of 7.7%. When tested again with a different assay: tPSA 2.1; %fPSA 13.7%

A brief review of the biology underlying the secretion of PSA and the genesis of the percentage of "free" PSA in the serum offers a useful background for analyzing this issue. The related

biology was nicely set forth in the review, "Biology of Prostate-Specific Antigen" by Bubley and Balk in JCO, January 15, 2003. They explain that as a result of androgen stimulation, mainly by dihydrotestosterone (DHT), the prostatic secretory epithelium secretes a 224-amino acid precursor protein, proPSA, into the ductal lumen where seven amino acid residues are immediately cleaved, thus creating the active mature proteolytic enzyme, PSA, whose purpose is liquifying semen. A modest proportion of this active enzyme is inactivated within the duct by enzymatic cleavage. As a consequence of various intraprostatic factors, a small proportion of both the active and inactive PSA leaks into the adjacent prostate vasculature where the active PSA is immediately complexed with an inhibitor of its enzymatic potential, alpha 1-antichymotripsin. However, as a result of cleavage alterations, the inactive form is **not** bound by this inhibitor and becomes the so-called "free PSA". Disturbances in normal glandular anatomy results in increasing amounts of PSA entering the systemic circulation. These factors may include increased internal pressure from BPH, and disruption of basement membrane and internal glandular architecture resulting from malignancy. Because the PSA isoforms that enters the circulation as a result of these disturbances *have bypassed transit through the ductal lumen* where "inactivation" occurs (the geneses of "free" PSA), a smaller proportion of the PSA leaking into the circulation is in the "free" form.

Finasteride, a steroidal analog of testosterone, functions as a reversible competitor to testosterone as the the substrate for type II 5-alpha-reductase, whose customany function is to convert testosterone into the 10 times more potent DHT. This competitive inhibition results in "a 75% decrease in serum DHT levels, an 80% decrease in intraprostatic DHT, and a 10% increase in serum testosterone,... finasteride's serum half life is about 8 hours,... and single doses as low as 0.2 mg depress serum DHT levels persisting for up to 4 days." (Brawley, Urologic Oncology Seminars, 21, 2003)

It is generally recognized that in men (who are not taking finasteride) and whose PSAs are between 4 and 10 ng/ml, a fPSA/tPSA ratio of >25% is associated with an 8% risk of PC, whereas a ratio <10% raises the risk to 56%. **However**, the focus of this article is upon the *effect of finasteride* upon the fPSA/tPSA ratio. This issue has been addressed in the literature in several ways.

Various authors have validated the observation that finasteride reduces the tPSA level by an average of 50% *without changing* the fPSA/tPSA ratio (Partin and Pannek, J UROL, Feb 1998, "Influence of finasteride on free and total serum prostatic specific antigen levels in men with *benign prostatic hyperplasia*" [emphases mine]. Kaplan, (Urology, Sept 2002, "PSA response to finasteride challenge in men with a serum PSA greater than 4 ng/ml and a previous negative prostate biopsy, preliminary study"), analyzed the change in total PSA in men who took 5 mg finasteride for one year. Results: no cancer was found on subsequent biopsy in men whose tPSA decreased 50% or more. In 19 men showing a decline in tPSA of only between 33% and 50% 6 cancers were diagnosed, and when the tPSA decline was <33%, 5 of 9 men (56%) showed cancer.

The article which addresses our example most specifically (Tarle, ANTICANCER RESEARCH 23, 2003) reported a study which involved 37 men who were prescribed 5 mg finasteride daily because of urinary symptoms resulting from enlarged glands of >60 cc. The fPSA/tPSA ratio was measured pre- and post-treatment. Twenty five men showed a mean reduction of 53% in tPSA (8.1 to 4.3 ng/ml) and their fPSA/tPSA ration was **unchanged** at 25%, consistent with the observation that in BPH the tPSA and fPSA should decline by a similar proportion. No cancer was found in this group during a 8-26 month follow-up. The baseline mean PSA of another 12 men was 9.9 ng/ml and their baseline mean fPSA/tPSA ratio was 20.1%. After 6

months of treatment the tPSA had only dropped to 7.2 ng/ml (a 28.3% reduction). *However*, the fPSA/tPSA ratio showed *only a 14% reduction* (20.1% to 17.4%) and in this group during a 4-19 month follow-up cancer was diagnosed in seven men (58%).

The proposed explanation for these observations is that in the presence of increasing BPH the benign tissue's contribution to tPSA increasingly overshadows the less conspicuous perturbation of the fPSA/tPSA ratio resulting from a concomitant, but comparatively smaller volume of prostate cancer. Finasteride effects shrinkage of the BPH tissue, thus diminishing its contribution to tPSA, and thereby unmasks the worrisome signature of possible prostate cancer.

Bottom Line: Analysis of the changes in the fPSA/tPSA ratio resulting from finasteride treatment can alert the physician to an increased risk of prostate cancer.

HORMONE INTERVENTION

Intermittent Androgen Deprivation: Promising Theory, Results Pending. (References available)
The honeymoon period of PSA depression that results from initial androgen deprivation conceals progressive subclinical cellular adaptations that eventually culminate into androgen insensitive prostate cancer. These are the adaptations that a strategy of intermittent androgen deprivation (IAD) strives to repress and postpone. Considerable research has focused on these adaptations and the results from the many Phase II trials have been instructive.

After the initial wave of apoptotic death of prostate cancer cells resulting from the initial steep decline of testosterone, the surviving cells promptly activate their survival "applications." The paucity of testosterone immediately upregulates genes expressing Bcl-2 and clusterin, anti-apoptotic proteins that promote cell survival; the testosterone deprived environment effects an increase in cell surface androgen receptors and greater cellular sensitivity to the diminished, residual testosterone; and cells resourcefully explore new signaling pathways by mutating the androgen receptor to widen its ligand preferences and lay the groundwork for alternative proliferative signaling via protein kinase A and the troublesome IL-6. The theory and hope underlying IAD is that the periodic pattern of testosterone restoration in IAD will abrogate these events, thereby prolonging disease control.

What has been learned from research and Phase II trials?

- IAD is feasible, and most likely is associated with survival outcomes similar to continuous androgen suppression. Validated questionnaires document a modest benefit in "quality of life".
- Initial treatment durations (the "on" periods) of 9 months or even >1 year produce the longest "off" periods.
- The most appropriate candidates for IAD are men whose PSAs fall to <.2 ng/ml (preferable "undetectable") after the initial "on" period of AD.
- Younger men; men with higher Gleason sums, or higher baseline PSAs are less successfully treated with IAD. The duration of the initial no-treatment time (the "off' period) appears to be shortened relative to higher baseline levels of serum PSA and less deep PSA nadirs, and these features are associated with higher Gleason scores (Bruchovshy).
- A single 3 month depot Lupron results in a median castrate level of testosterone of 6 months.

- The duration of "off" treatment periods gradually shorten and vary with the factors listed above, but initial "off" periods of 9 to 16 or more months are common.
- The PSA signal for restarting AD set forth in the different protocols varies widely from 3 ng/ml to 20 ng/ml PSA.
- Bruchovsky studied the relationship of testosterone and PSA in cycles of AD and found that the recovery of testosterone precedes the rise of PSA by approximately 6 months. He observed that if the PSA rise precedes the testosterone recovery then androgen insensitivity is likely developing.
- Under study is the possibility that continuous finasteride will lengthen the "off" period, and in some studies finasteride prolonged the no-treatment period from 24 weeks (without the medication) to 80 weeks. There is some evidence that rapid re-exposure to testosterone of an androgen deprived cell will reawaken apoptotic potential (Bruchovsky) and this area is under study as a technique to maintain cell sensitivity to AD and prolong remission.

The currently active nationwide omnibus Phase III **randomized** protocol (i.e., SWOG 9346, & ECOG, et.al.) tests IAD in men with metastatic disease. Activated in May 1995 with a goal of more than 1500 registrants, it prescribes the combination of Zoladex and Casodex for all men for a period of 7 months. Participants achieving a PSA of $\leq$ 4 ng/ml are randomized between IAD or continuous androgen deprivation. For the IAD group a PSA of >20 ng/ml is the signal for restarting 7 more months of treatment with cycles repeating as long as the study requirements are met. The results are several years away.

At the AUA meeting in May 2003 a German group reported preliminary results from the first **randomized prospective** trial comparing IAD to continuous (C) treatment. The protocol design compared Lupron administered either intermittently or continuously in men experiencing their first PSA relapse (PSA $\geq$ 1 ng/ml) following radical prostatectomy, 82 men (IAD) v. 68 (C). All men initially received Lupron for 6 months, and those who achieved a PSA <0.5 ng/ml were then randomized between the two arms of the study. In the IAD group treatment was restarted when the PSA levels became 3 ng/ml. The median pretreatment PSA in the IAD group was 3.5 and the mean off-treatment period in the IAD group was 9.9 months in cycle #1 and 6.1 months in cycle #2. Normal testosterone levels were regained in the IAD group 4 months after treatment cessation. At a current median follow-up of 24 months there is no significant difference between the two groups in time to disease progression. However, this is much too short a period of follow-up to support any overall conclusions.

Bottom Line: An intermittent androgen deprivation treatment strategy in relapsed PC offers important theoretical advantages, but superiority over continuous androgen deprivation has not yet been established.

IN BRIEF

- Beware The Bicycle Seat: "Cycling for fifteen minutes (301 men tested immediately after exercising on a bicycle ergometer) has been shown to increase PSA concentrations up to threefold, but other forms of exercise do not seem to have any effect" (Oremek, Clin Chem 1996). However, in UROLOGY, JUNE 2003, Luboldt reports no change in PSA in 37 men when tested one hour after a 13-mile bicycle ride. Luboldt speculates the discrepancy between the two studies may be explained by the different times of sampling combined with

a short half-life of PSA, especially of free PSA...(Hint: Don't immediately test your patients who ride their racing bikes to the office)

- Decadron And Il-6: Skepticism that Decadron lowers PSA by reducing adrenal androgens has been supported by the finding that Decadron significantly suppresses serum IL-6. IL-6, a cytokine, has been found to function as an alternative means of promoting PC growth and PSA elevation in "hormone refractory" PC by shortcutting the usual pathway for androgen receptor signaling. (The Prostate, Volume 56, p. 106)
- Cutting Off The Growth Signal: Vapreotide, a somatostatin analog which interrupts the proliferative stimulus of growth hormone, led to clinical improvement in 8 of 13 "hormone refractory" PC patients (6 with a mean PSA drop of 71%) and brought about symptomatic improvement in bone pain. Three men were in continuous remission for 79, 45, and 45 months. (The Prostate, Volume 56, p.183)
- Single Case, But Interesting: Xeloda (capecitabine), an oral prodrug of 5-Fluorourail commonly used to treat colon cancer, led to a complete remission in a symptomatic hormone refractory PC patient. (Urology, 2003 Feb: p.462)
- Radiobiology - Importance Of Vasculature: Writing in SCIENCE, VOL 300, 16 MAY 2003; p 1155. ("Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptoses"), MSKCC and Cornell researchers present evidence supporting "microvascular damage as a key mechanism in tumor response" associated with radiotherapy. Their work offers an alternative paradigm to the current consensus that DNA damage and mitotic death result from direct interaction of radiation with tumor cells.
- The Vasculature Is The Target: Increasingly a tumor's blood supply is recognized as vital to its inception, growth and survival. Thalidomide (T) blocks three important angiogenic agents that promote the development and sustenance of tumor capillaries: interleukin-6 (IL-6), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF). The British Journal of Cancer, March 2003, reported a study using 100 mg T in 20 men with androgen insensitive PC in which 15% showed a $\geq$ 50% decline in PSA (6 of 16 treated for 2 months had a median PSA fall of 48%). In another study of 63 men using 200 mg/d, 28% showed a PSA decline of >40%. When T at 200 mg/d was combined with taxotere (30 mg/m2 weekly q 3 wks), 19 of 36 (53%) had a PSA fall of $\geq$ 50%, whereas only 6 of 7 (35%) receiving taxotere alone met that benchmark. (Seminars Oncol Aug 2001)
- A Paradox - And A Possible Explanation: As men age the serum testosterone often gradually falls to subnormal levels (<3 ng/ml), but, perhaps paradoxically, as men age the incidence of clinical prostate cancer increases. It's well recognized that subclinical PC increases substantially with aging. Some factors must boost the latent disease into the clinical range. A study from Vienna evaluated men with clinically diagnosed PC and divided them into two groups based on < or > 3 ng/ml testosterone. The men with subnormal testosterone (< 3 ng/ml) at diagnosis had lower PSAs (18 v 27) and higher Gleason scores (7.4 v. 6.0). The subnormal group showed greater androgen receptor density on the PC cells and significantly higher tumor vessel density in the tumor (p=0.007), suggesting enhanced malignant potential associated with lower testosterone levels. (Schatz, J Urol, April 2003) These finding could be one of the explanations for the more aggressive cancers found in the finasteride group in the Postate Cancer Prevention Trial recently reported in the NEJM.