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Contents

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HORMONE INTERVENTION: INTERMITTENT ANDROGEN SUPPRESSION: A Work in Progress (*From a birthday card sent to me by my wife, "Life's big problems - where to start and when to stop."*

The details of the application of intermittent androgen suppression (IAS), just as is true for active surveillance, are being actively worked out. Many differing options are employed. Currently, the important issues under study include: the selection of optimal patients to be treated with IAS, choosing the PSA point for therapy initiation ("where to start"), the initial duration of therapy, identifying early indicators of possible success or diminished benefit from IAS, and "when to stop" the therapy "holiday" and resume androgen suppression. A wide variety of recommendations exist for each of these issues.

An overall review of IAS was presented in the PCa Commentary in the Jan/Feb 2010 issue ("Intermittent Hormone Therapy: Confirmation of Effectiveness"). It summarized the current consensus that there is no difference in outcome between IAS and continuous androgen suppression. This current analysis will focus upon the *details* of IAS application.

For those clinicians managing patients using IAS, an essential article to read is "The continuing debate: Intermittent vs. continuous hormonal ablation for metastatic prostate cancer," by Gleave, Klotz and Taneja, Urologic Oncology 27 (2009). This presents a summary of a debate on this issue at the Spring Meeting of the Society of Urologic Oncology. (And contrary to the article's title, the main focus is on the use of IAS in "men with advanced prostate cancer ***except*** those with high-risk features including PSA >20, or bone metastatic disease.)

A second very informative overall review is "Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature," by Abramamsson, European Urology Jan. 2010.

Who are the optimal candidates for IAS?

The best choices are men experiencing PSA relapse with lower pre-primary treatment PSA values who exhibit low- to intermediate-risk cancer, non-bulky tumors, having no spread to lymph nodes or bone, and PSA values of < 20 ng/ml. Gleave and others cite *not achieving* a PSA nadir value of <4 ng/ml after 6 months of induction as a predictor of a poorer outcome. Gleave reports that the benefit of IAD is less in this group and IAD not advisable in men with high-risk disease, PSA doubling time of <9 months, and high-grade cancer and bone metastases. "The off-treatment interval is short in these patients."

Evan Yu et al.(JCO June 2010) document that a first holiday period of <40 weeks, as compared to >40 weeks, predicts a nearly 3 times shorter interval to castrate resistant prostate cancer and a 3.8 times greater risk for death.

Start point for ending induction and duration of induction

In the debate with Dr. Gleave, Dr. Klotz makes a contrarian point of interest. He argues that he would advise withholding the ***start*** of induction until the PSA rises to >20 in men <70 yrs. and >50 in men older than 70 yrs., Based on a European study that "showed that overall survival improved in men under 70 years old when treatment was initiated at a PSA over 20, and in men over 70 years old at a PSA over 50." If the purpose of IAS is to minimize treatment side effects, Klotz argues, then the optimal strategy would be to avoid any exposure to androgen suppression for as long as possible.

More commonly, however, treatment is started earlier since a Canadian study showed that in those men starting suppression at PSA >20 the duration of the first "holiday" was 39 weeks compared to 90. Variety abounds on this issue.

Conventionally, the duration of induction is between 6 and 9 months (Gleave). However, induction was 3 months as reported in one of the few large randomized Phase III studies treating men with advanced prostate cancer (da Silva, European Urology, 2009). This study involved men having ***no primary intervention with RP or RT***; and a mean baseline PSA 1.2 ng/ml. with 22% having a PSA >4. Only those achieving PSA <4ng/ml were eligible for randomization. Shaw (Surgical Oncology,2009) concluded: "A PSA nadir of <1 ng/ml has been shown to be the best determinant of when it is safe to stop treatment. This level can be achieved in as little as 3 months in most patients with localized disease."

PAS level for restarting androgen suppression after an "off" interval

First, a bit of biology: Gulley (J Urol,May 2005) reported on testosterone (T) recovery in 80 patients measured from the time of administration of the second of two 3 monthly Lupron shots. The median time to T recovery to >50 ng/ml (non-castrate level) or more was 12.9 weeks, and for T normalization (212 ng/ml or greater) 16.6 weeks.

These figures for T recovery are relevant since, as noted by Shaw: "Preclinical work using castrate mice with hormone sensitive prostate tumors demonstrated that pulses of testosterone significantly ***delayed*** the onset of androgen independent growth and PSA production in these mice." Studies suggest that conditions of low testosterone promote adaptations in the androgen receptor that facilitate

its stimulation by factors other than testosterone and lead to androgen independence. Theory suggests that pulses of testosterone will reset the system back to androgen dependence, and restore the original status of testosterone dependence favorable for another effective round of androgen suppression. Unfortunately, clinical studies to date have shown only equivalence, and not superiority, for IAS compared to continuous androgen suppression, even though "off" periods of a year or more should provide ample periods of testosterone re-exposure.

Phase II studies have shown that the use of finasteride during the "off" period doubled its duration (Scholtz, J UROL, May 2006).

There is little consensus regarding the PSA value for restarting androgen suppression. Shaw reports restart values ranging from 5 to >20 ng/ml, but cites data that resuming therapy at a PSA >15 carries an increased risk of developing CRPC and 1.6 times the risk of death. Da Silva's large randomized study used the >20 PSA restart point as did several European studies.

Yu, Higano, Nelson et al., in their June JCO study establishing the importance of the duration of the first "off" period used a quite stringent PSA restart point after the "holiday:" 1 ng/ml for men after surgery and 4 ng/ml following radiation.

10 ng/ml PSA was the threshold chosen by Bruchovsky, Klotz, and Gleave et al. (Cancer, July 15, 2006) in their phase II study of IAS post-radiotherapy.

BOTTOM LINE: What might be a reasonable model to follow as consensus on these issues forms? In 1998 the Southwest Oncology Group, the NCI of Canada, and the NCI Clinical Trial Group initiated a Phase III trial (not yet reported) for men in PSA relapse following radiotherapy comparing IAS to continuous therapy. An 8 month induction using combined androgen blockade was offered when the post-radiation PSA rose to >3 ng/ml. For those men randomized to IAS the "off" period commenced at PSA nadir of <4 ng/ml and IAS was resumed when the PSA rose to >10 ng/ml.

CASTRATE RESISTANT PCa: BICALUTAMIDE 150MG: Promising Results as Salvage Therapy for Nonmetastatic Castrate Resistant Prostate Cancer

An on-line report by Lodde et al., UROLOGY. 2010 Mar 17 [Epub ahead of print] described the outcome of bicalutamide 150 mg/day in 38 men with CRPC all of whom already had received one or more types of prior antiandrogen therapy. The median PSA at the start of bicalutamide was 1.5 ng/ml and the median PSADT leading into treatment was 5.24 months.

Responses: 47% had PSA decrease of ≥50% with a 22.9 month median duration of PSA control. The 18.4% of men whose PSA decline was ≥50% but <85% showed a median duration of response of 18.5 months; for those with PSA decline >85% the median duration was 37.4 months. Termination of response was determined by a PSA rise above nadir by ≥25% or 2 ng/ml above nadir.

Only one of the six men having had prior bicalutamide therapy at 50 mg/day responded to the stepped-up dose of 150 mg., and this suggested to the authors that this strategy was not effective in this group.

For those men having a ≥50% decline in PSA the median time to metastases was 52 months. Second-line hormone therapies as salvage for men whose PSA rises despite castrate level of testosterone include: ketoconozole, corticosteroids, all types of antiandrogens, and diethylstilbesterol. The outcomes from these interventions are generally inferior to those reported in this study.

BOTTOM LINE: Clinicians managing prostate cancer eagerly await final results and FDA approval of already promising performances for abiraterone and MDV-3100. However, this study by Lodde offers a new and available arrow in the quiver to aim at castrate resistant prostate cancer.

STATINS FOR PROSTATE CANCER: Are they really beneficial?

It would be very satisfying to find that statin drugs, used so nearly universally for the prevention of cardiovascular disease, would interrupt prostate cancer in any or all phases of the disease. In vitro

studies and many observational clinical studies have come close to establishing the likelihood of benefit in *some* phases of prostate cancer.

A strong biologic foundation exists to support the deterrent effects of statins mediated through both cholesterol and non-cholesterol (anti-neoplastic) mechanisms in inhibiting the formation and progression of prostate cancer. An excellent review of this issue is "Rationale for Statins in the Chemoprevention of Prostate Cancer," Hamilton and Freedland, Current Urology Reports, 2008, 9.

Statins decrease the body's production of cholesterol, especially low-density lipoprotein cholesterol (LDL). Although research has not found an association between statin use and androgen levels, "it remains conceivable that statins, by lowering intraprostatic cholesterol levels, could lower intraprostatic androgen levels". (Hamilton)

Less obvious are the non-cholesterol mediated consequence of cholesterol depletion that results in impairment of intracellular signaling causing inhibition of prostate cell growth, decreased (by 72%) tumor inflammation, lower oxidative cellular stress, and both impaired angiogenesis and tumor invasion. Interestingly, COX2 inhibitors (such as Celebrex) are synergistic with statins in these effects.

It would appear that the reported benefits of statin medication accrue to all the current brands. An excellent primer on this overall issue is "Statins and prostate cancer prevention: where we are now, and future directions," Murtola et al, 2006, Nature Clinical Practice.

What have clinical studies shown?

1. *Statins and prostate cancer prevention:* Although the jury is still out on this, the consensus based on most clinical trials is that to date overall prostate cancer risk is not lessened by statin use. Thus, currently there is insufficient evidence to prescribe the drug for this purpose.
2. *Statins and PSA levels:* Statin use lowers PSA - but studies vary in the extent of decrease. Hamilton et al. (JNCI 2008 Nov) reported a lowering by 4.1%. However, those men with the highest reductions in LDL, i.e. >41%, experienced a 17.4% reduction in PSA. Representative reductions from baseline PSA to post-statin values in various reports are: from 7.3% to 5.2%, and 6.9% to 6.2%.
3. *Statins and advanced prostate cancer at diagnosis:* Murtola addresses this point succinctly: "Well-designed clinical studies report a decreased risk of advanced prostate cancer in statin users. This association is dependent on the duration and quantity of statin use," with the reduction seen most for men diagnosed with poorly differentiated tumors. In their study of 2579 men 316 were diagnosed with "regionally invasive, metastatic or fatal" disease. Those reporting statin use of <5 years showed a 40% reduction of advanced disease, and those on statins for >5 years had a 74% decrease.

   Hamilton reported T1 stage in 67% of statin users v. 58% for non-users.

4. *Statins and prostate cancer progression:*

Progression in men following radical prostatectomy:

At the recent AUA meeting Hamilton reported that post-prostatectomy statin users had a 30% reduction in prostate cancer recurrence. CaPSURE data presented by Katz at the AUA meeting showed that among the 4611 men who underwent radical prostatectomy, statin users had a 65% reduced risk of all-cause mortality; among 2431 men treated with radiotherapy the statin users had a 41% decrease risk of all-cause mortality.

Progression in men following radiation therapy:

Zelefsky, Katz et al. (Int J Radiat Oncol Biol Phys. 2010 May) followed 1711 men with clinical stage T1 - T3 cancer of whom 23% were taking statins. "The 5- and 8-year PSA relapse-free survival (PRFS) rates for statin patients were 89% vs. 80%, compared with 83% vs. 74% for those not taking statins. The benefit, however, in PRFS was seen only in high-risk patients, where a 48% reduction was seen.

In a recent JCO report, June 2010, Gutt reported that men treated with curative intent radiotherapy found that statin users vs. non-users in all risk categories had significant improvements in freedom from biochemical failure, freedom from salvage androgen therapy, and improved relapse-free survival.

BOTTOM LINE: Although no randomized clinical trial has addressed these issues, nonetheless a persuasive body of laboratory and clinical data suggest a useful role for statins in reducing the stage and aggressiveness of prostate cancer at diagnosis and improving outcome after initial therapy.

ANTIANDROGENS IN ASSOCIATION WITH INITIATION OF LUPRON ADMINISTRATION: Are they always needed? An evidence-based contrarian argument against their routine use.

A well-recognized surge of testosterone (approximately 2-fold) follows in the first week after the initiation of an LHRH agonist, such as Lupron. But as cited by Bubley (Urology. 2001 Aug: "Is the flare phenomenon clinically significant?"), "There is no clear consensus as to whether antiandrogens should be routinely given to all patients during the first month of LHRH therapy to prevent flare responses." When LHRH analogues are used in the neoadjuvant setting of non-metastatic cancer, despite the biochemical evidence of a testosterone surge, "these patients are at very little risk for clinical flare responses" (Bubley). In patients with metastatic disease, however, a week of antiandrogen therapy prior to Lupron usage has been considered nearly required, "despite a lack of randomized controlled clinical trials to justify their use ..." (WK Oh, UROLOGY. March, 2010 - see below).

William Oh, now Chief, Division of Hematology and Medical Oncology, Mount Sinai School of Medicine, and Keating, et al. offer a thoughtful analysis of this requirement for dual therapy: "Does Oral Antiandrogen Use Before Leuteinizing Hormone-releasing Therapy in Patients with Metastatic Prostate Cancer Prevent Clinical Consequences of a Testosterone Flare?" They find the evidence for its use lacking.

Their report was based on a retrospective study of 1566 men with *metastatic cancer* in the Veteran Affairs Medical Centers. Of these, 79.5% received an antiandrogen - 48.5% of whom received the antiandrogen for 7 days or more before the LHRH agonist, and 31.4% between 0 and 6 days prior. And 20.5% received no antiandrogen.

Their conclusions: there were no differences in outcome as regards "fractures, spinal cord compression, radiation therapy, bladder outlet obstruction, or narcotic prescriptions (all $P \leq .05$)." "Rates of spinal cord compression or fractures were <1% in the first 30 days after the beginning of LHRH agonist therapy regardless of antiandrogen use." [The 30 day interval was chosen because that is the median time for the post-LHRH testosterone surge levels return to baseline.]

Their findings are in marked contrast to the often cited 10% complication rate for clinical flares following LHRH agonist monotherapy (range 4% - 63%) in earlier studies.

A basis for biologic plausibility supporting Oh's findings may lie in the "Saturation Theory" presented by Morgentaler and Traish (EUROPEAN UROLOGY. 2009 - cited in detail in PCa Commentary, March/April 2010) where data was presented to indicate that in *non-castrate* men testosterone levels higher than approximately 120 ng/ml are "excess" and have no effect on prostate cancer's growth.

What may surprise clinicians is that the "surge" *does not* raise PSA levels! Clinicians are accustomed to equating increases in prostate cancer growth with rises in PSA values. The thought would therefore follow that if the "surge" of a testosterone flare causes cancer growth and complications, then the PSA should rise during the flare. This graph below from their article suggests a lack of association.

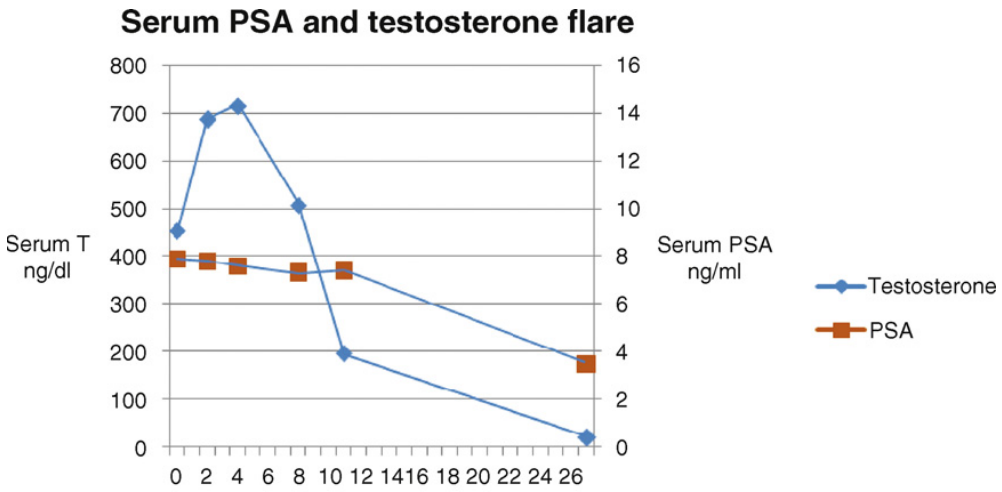

Fig. 4 Serum prostate-specific antigen (PSA) level is unchanged during testosterone (T) flare. Men with stage D prostate cancer were treated with luteinizing hormone-releasing hormone (LHRH) agonists and T, and PSA levels were determined on selected days following injection. Despite an increase in serum T of approximately 50% over baseline, no increase in PSA level was seen.

Adapted from Tomera et al, J Urol 2001;16:1585-9

Crawford and Eisenberger (NEJM. 1989) reported early evidence of clinical consequences associated with the testosterone flare in a study of combined androgen blockade v. monotherapy with leuprolide. Pain was reported in 11% of patients on CAB vs. 5% taking placebo. Subsequent studies seemed to give support to this unwelcome association. An understandable drawback of Oh's retrospective study (and Crawford's) was the lack of identifying correlations of (say) back pain with the location and extent of spinal abnormalities on bone scans. This correlation would have given guidance in relating the extent of disease with spinal complications.

The 2010 version of NCCN Clinical Practice Guidelines for prostate cancer (under "Principles of Androgen Deprivation Therapy," page 176) give clinicians ample room for exerting clinical judgement: "Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued for at least 7 days for patients with *overt metastases* [emphasis mine] who are *at risk* of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone." Thompson (Rev Urol. 2001; Suppl 3) advises combined therapy when initiating treatment in men with advanced disease, or those with very high PSA levels.

BOTTOM LINE: Clearly, not every patient with metastatic disease requires an antiandrogen with the initiation of LHRH agonist therapy; and research by Oh et al. gives a useful contemporary perspective on this issue. Careful selection and clinical judgement will identify those men in whom it is safer to employ the combined therapy.