SEATTLE PROSTATE INSTITUTE

PCa Commentary

Vol. 47: Sept.-Oct. 2007

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Determining Dosing Intervals For Lutenizing Hormone Releasing Hormone Agonists Based On Serum Testosterone Levels: A Prospective Study

As noted by a group of authors from the Department of Urology, Kaiser, Los Angeles, (title above) in J.UROL, June 2007, the manufacturer's recommended dosing of a 22.5 mg Lupron Depot at 3 month intervals is not evidence based. Five percent of patients so dosed do not achieve castrate testosterone (T) levels (50 ng/dl or less), and the majority only rise above that level in several to many months beyond a 3 month period. These researchers sought to individualize dosing based on a patient's serum testosterone level and retreated with 22.5 mg of Lupron only when the serum T level exceeded 50 ng/dl.

Forty-two men naive to hormone intervention were studied (3 were metastatic based on a positive bone scan): median age, 78.5 years; median pretreatment T, 15.5 ng/ml; average Gleason score, 7; and median post-induction PSA, 0.745 ng/ml. The regimen was initiated with 2 consecutive 3-month 22.5 mg Lupron doses, and if serum T level fell to castrate range, then the serum T level was monitored monthly, and re-treatment was administered only when the serum T exceeded 50 ng/dl. "If there were 3 consecutive increases in PSA despite serum testosterone of 50 ng/ml or less," the patient was considered hormone refractory, removed from the study, and referred to medical oncology. During the 18 month follow-up 3 patients were considered hormone refractory.

The study measured the duration of castrate levels of T for each patient "based on the time from the last [induction] injection to the first non-castrate serum T level (more than 50 ng/dl)."

Findings: "...the most significant finding of this study is that not a single patient required dosing of the LHRH agonist more frequently than 5 months." The median duration was 6 months, and (abstracted from the graph) 27 were retreated at 7 months, 12 at 8 months, and "One patient had prolonged castration and had a dosing interval of 12 months."

The authors calculated the significant savings that would accrue from this regimen. At Kaiser a 22.5 mg Depot Lupron costs $1878.26 (considerably less than in the private sector!). The average annual cost of the T-based regimen was $7,316 vs. $3,973 for 3-month dosing.

An EDITORIAL COMMENT in the article added perspective by noting that "Although of interest, this [T-based] approach is being overshadowed by the use of intermittent ADT [see July/August PCa Commentary for discussion of intermittent androgen deprivation therapy]." Cited was the JCO ASCO Annual Meeting Proceedings, Abst. 5125 which reported at 2.8 years of follow-up an estimate that 82% of the 854 men on the intermittent arm remained free of therapy for one year, and 60% therapy-free for 2 years. "Patients with [pre-therapy] PSA < 1 ng/ml are off therapy for 2.5 years while 60% of patients with PSA 1-4 ng/ml are off therapy for 1.5 years." The study was too immature for progression or survival data.

Quality Of Life Issues Related To Testosterone-Based Dosing And Intermittent Androgen Deprivation (Iad)

Since the strategy of testosterone-based re-dosing, albeit at 6 months or longer, effectively achieves continuous castrate levels of serum testosterone, associated symptoms of androgen deprivation are not avoided by this strategy. Oefelein (J UROL 2003, Jan) made this conclusion in his small control-crossover trial of testosterone-based re-dosing: "However, by study completion overall health related quality of life was equivalent regardless of dosing method."

A regimen of IAD does yield benefits in quality of life as a consequence of withholding the subsequent administration of (say) Lupron until a PSA of 4, 10, or even 20 ng/ml is reached - various studies have used different trigger points. This target PSA trigger for re-treatment lies well beyond - many months, and possibly over a year - the point at which a man exceeds the castrate level of serum T and then slowly regains a functional T level. Oefelein nicely documented the time relationships of the rise of T following a single 3-month administration of and LHRH agonist in his study of 13 men, median age 65 years. The baseline T was 400 ng/ml. The testosterone levels at 3,6,7,9,12,15 and 18 months after therapy were 0.1, 0.2, 0.7, 1.8, 1.9, 2.1, and 2.3 ng/ml, respectively. The median duration of suppressed serum T (20 ng/ml or less) was 6 months. However, "The median duration of hot flashes and sweats was 13.6 months."

Da Silva et al.[cited above in EDITORIAL COMMENT] reported QOL aspects of their study of intermittent vs. continuous MAB and noted, "After randomization, sexual activity increases in the intermittent group to 32% (6 months), 32% (12 months), 24% (24 months), while in the continuous arm the corresponding percentages are 19%, 20%, 6%, respectively. In their earlier 2006 report, abst. 4513, they reported hot flashes at 30% in the continuous arm vs. 20% in the IAD group. Their conclusion: "There is no evidence that intermittent therapy leads to a significant elevated hazard of dying (p=0.79) or greater subjective or objective progression (p=0.52) and with less impact on quality of life and less medication. Patients with PSA <2 ng/ml at randomization have spent a median of 82% of their time receiving no therapy."

Standard Androgen Suppression Does Not Fully Ablate Intraprostatic Androgens

Somewhat surprisingly, castrate levels of *serum* testosterone do not produce rock bottom androgen levels *within* the prostate, with BPH or cancer. The intraprostatic T and dihydrotestosterone (DHT) levels are only reduced to 20% to 30% of normal, and those amounts are quite sufficient to drive the androgen receptor. Page et al. (J Clin Endocrinol Metab. 2006 Oct.) reported that with androgen suppression by an LHRH agonist "The mean decrease in serum T was 94%, whereas prostatic T and DHT levels were 70% and 80% lower" [than normal, respectively] ... [and] "there were no detectable differences in prostate epithelial proliferation, apoptosis, prostate-specific antigen, and androgen receptor (AR) expression." Similar findings were reported by Mostaghel et al. (Cancer Res. 2007, May). After neoadjuvant ADT of 1 and 9 month periods the tissue androgen levels in the subsequent prostatectomy specimen were reduced by 75% and many androgen-responsive genes, including the AR and PSA genes, were not suppressed after both periods of ADT. The authors speculated that "Suboptimal suppression of tumoral androgen activity may lead to adaptive cellular changes allowing prostate cancer cell survival in a low androgen environment."

What is the source of this 20% residual intraprostatic DHT that survives androgen suppression? This was studied by Suzuki et al. in "Importance of the intracrine metabolism of adrenal androgens in androgen-dependent prostate cancer" (Prostate Cancer Prostatic Dis. 2007 Mar) in which they showed that "adrenal androgen precursors do not directly interact with androgen receptors (ARs) but are converted to DHT via the intraprostatic metabolic pathways [i.e. by 5alpha-reductases]." Consideration of this mechanism "suggests the use of combined therapies that target ARs and prevent the formation of DHT within prostate cancer cells to achieve optimal therapeutic efficiency."

Would Concomitant Dutasteride Strengthen Standard Adt?

Although the 5alpha-reductases might be considered weak compared to LH-RH agonists and anti-androgens, Wurzel et al. (Prostate Cancer Prostatic Dis, 2007, Oct.) found that the dual 5alpha-reductase inhibitor, dutasteride at 0.5 mg/day, reduced intraprostatic DHT by 94% in association with reducing serum DHT by 93%, although there was a slight reciprocal increase in intraprostatic T. (On the contrary, *serum* testosterone *increases* during dutasteride treatment with one study showing an increase of 19%.) The Wurzel data was accrued in a study of 43 men who received dutasteride vs. placebo for 3 months prior to surgery. Andriole et al. (J Urol. 2004 Sep) found that 5.0 mg [the usual clinical dose is 0.5 mg] of dutasteride led to a 97% reduction in DHT compared to placebo after a 6 - 10 week course prior to surgery. A decrease in microvessel density and an increase in apoptosis caused the authors to ponder whether dutasteride "can cause regression of some cancers."

The importance of reducing intraprostatic DHT to the lowest achievable level was emphasized by Singh et al. in "Combinatorial androgen receptor targeted therapy for prostate cancer" (Endocrine-Related Cancer, 2006,13). "Prostate cancer cells express modest levels of type two 5alpha-reductase [inhibited by finasteride] but have significant expression of the type one 5alpha-reductase." Dutasteride inhibits both types one and two 5alpha-reductase isoenzymes. Singh points out that although the intraprostatic T is significantly lowered by LHRH agonists,"the low level of testosterone remaining can be amplified by the conversion of testosterone to DHT catalyzed by intraprostatic 5alpha-reductase." Singh finds validity in "the use of a 5alpha-reductase inhibitor, such as dutasteride, in combination with a LHRH analog to further lower DHT levels within prostate cancer", and this approach is currently being tested by

GlaxoSmithKlne in men with metastatic cancer who had a rising PSA level while on LHRH monotherapy.

Suggestive research is developing indicating that dutasteride, unlike finasteride, may address prostate cancer directly (in addition to depleting DHT). McCrohan's work (CANCER 2006 Jun) along with other researchers have found that dutasteride "induced a dose-dependent increase in apoptosis in [some of] the androgen-sensitive prostate cell lines ... and in the androgen-expressing PC3 (AR2) cell line."

Intermittent Androgen Deprivation With An 5alpha-Reductase Used In The "Off Treatment" Period

An effort to prolong the duration the "off treatment" period has been under study using finasteride by a variety of researchers. Scholz et al, (J Urol. 2006 May) retrospectively analyzed 101 men treated with IAD over a 9-year period, 60 of whom received finasteride during the time off period, and 41 with no finasteride. The mens' clinical stages were T1c-T2a in 51, T1b-T3b in 11, PSA relapse in 29, and T3c, D0 or D1 in 10. Median PSA was 7.6, median Gleason score was 3 + 4, and the median follow-up was 8.75 years.

It's worth presenting the methodology of this study since the schema employed may serve to inform future protocols using dutasteride. Induction was achieved with an LHRH agonist combined with either 50 mg/qd bicalutamide or flutamide 250 mg TID, and continued until the PSA was below 0.1 ng/ml, usually requiring 13 months of therapy. Time off therapy was measured from the date at which the PSA first exceeded 0.1 ng/ml until re-administration of ADT. The PSA trigger of re-treatment was arbitrarily chosen at PSA of 2.5 ng/ml for the finasteride group (in acknowledgment of the 50% reduction in PSA associated with a 5alpha-reductase inhibitor) and 5.0 ng/ml for the control group. To be eligible for analysis a man's testosterone had to recover above 150 ng/dl by 12 months from the point at which the PSA first exceeded 0.1 ng/ml. "AIPC [androgen insensitive prostate cancer] was defined as failure to attain an undetectable PSA of less than 0.1 ng/ml with the reinstitution of [ADT] while testosterone remained less than 50 ng/dl."

Study findings: Median time off therapy for the finasteride group, 31 months; and for the control group, 15 months.

As yet there are no published trial results of intermittent androgen deprivation using dutasteride in the "off periods". However, this regimen is an idea whose time has come because of its sound basis in science. We should look forward to a protocol studying it in the near future.

ACKNOWLEDGMENTS: Special thanks to Charles Heaney, Executive Director of the King County Medical Society, who continues to find time in his busy workload to edit and format the Commentary. It would be nearly impossible to do research for the Commentary without the generous support of the Swedish Hospital librarians, Mike Scully and Bob Hollowell. And lastly, thanks to Eryn Mitchell at the Seattle Prostate Institute who prints and mails this publication, and Bill O'Reilly who places the copy on the Web.