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HORMONE INTERVENTION: Androgen Deprivation, Diabetes, and Adverse Cardiovascular Events

Two recent large studies document that androgen deprivation - even short term - significantly increases the incidence of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death in men receiving GnRH agonists.

Keating et al., JCO Sept. 2006, based their analysis on SEER data of 73,196 men 66 years or older with locoregional prostate cancer, 36.3% of whom received a GnRH agoinst, 6.9% bilateral orchiectomy, with the remainder having received no hormonal intervention. The effect of duration of therapy on complications was analyzed by grouping duration of therapy for 1 to 4 months, 5 to 12, 13 to 24, and 25 months or longer; and consideration was given to the fact that hypogonadism usually persists for as long as 6 months (and as long as 2 years depending on baseline testosterone value and duration of therapy) following a short course of ADT. "On

average men treated with GnRH agonists were on treatment for 40% of the time from diagnosis through censoring..."

The hazard ratios associated with the increased risk of diabetes was 1.44, for coronary heart disease, 1.16; myocardial infarction, 1.11; and for sudden cardiac death, 1.16. An important, and perhaps unexpected, finding was: "... an increased risk of diabetes and coronary heart disease was evident in men on GnRH agonist therapy for as few as 1 to 4 months," indicating that these risks "occur early and persist with continuous treatment."

The adverse association of GnRH agoinst therapy with these complications is "biologically plausible" because these agents "significantly increase fat mass, fasting insulin levels, and decrease insulin sensitivity" and adversely change serum lipoproteins and arterial stiffness - and do so even after short term usage. Of interest: "We found that orchiectomy was associated with a greater risk of diabetes, but not coronary heart disease, mycardial infarction, or sudden cardiac death."

Their conclusion: "Our findings support the need for discussion of the potential cardiovascular risks of this [GnRH] therapy before starting treatment" and point up the need to initiate strategies to "mitigate modifiable risk factors for diabetes and coronary heart disease" in men requiring GnRH agonist therapy.

D'Amico et al. (JCO, June 10, 2007), "Influence of Androgen Suppression Therapy for Prostate Cancer on the Frequency and Timing of Fatal Myocardial Infarctions," concluded that men 65 years or older who were treated with 6 months of adjuvant ADT (GnRH agonist/flutamide) experience earlier onset of *fatal* myocardial infarctions (MI) than those receiving no ADT (p=0.17). The study combined data from three randomized trials - a US trial, 206 men; an Australian/New Zealand trial, 802 men; and a Canadian trial of 364 men. In the authors' opinions the treatment/no treatment arms were well balanced for cardiovascular risks. The US trial was specifically stratified for smoking history, hypertension, diabetes mellitus, BMI and age. The median follow-up ranged from 4.8 years to 6.7 years. The shorter time to fatal MIs was illustrated by the observation that "before the first fatal MI occurred at 21 months in the men [≥ 65 years old] randomly assigned to receive *no* AST, 44% (eight of 18 MIs) of all observed fatal MIs had occurred in men in this age group randomly assigned to receive 6 months of AST," and their data suggested, but further confirmation is required, that this risk might occur with as little as three months of therapy.

The report offered an additional important fact that has not been apparent in the literature: "The Early Prostate Cancer Trial found an unexpected *decrease* in overall survival in men with a median age of 69 years who were on a watchful waiting program for clinically localized prostate cancer and who were randomized to receive 150 mg of the antiandrogen bicalutamide by mouth daily for a median of 4.4 years compared to placebo." Although bicalutamide raises the testosterone level, "evidence now exists that the protective effect that testosterone may have on the development of atherosclerosis is blocked by bicalutamide's antagonism of the androgen receptor."

Further studies with proper stratification will be required to ascertain if the metabolic changes from ADT "precipitate an MI in a predisposed man." D'Amico, as did Keating, counsels cardiovascular evaluation prior to the start of ADT. The findings in these two studies impinge on clinical management because of the increasing use of ADT in general, and its beneficial use for men at high risk for recurrence in particular.

PREVENTION & DIET: Lycopene and Prostate Cancer Prevention - A Less Optimistic Report

If you are loading up on lycopene as a hedge against prostate cancer, it better be largely because you really like tomatoes. The lycopene stock is highly volatile, with a recent sell-off due to a large study conducted by the Fred Hutchinson Cancer Research Center, "Serum Lycopene, Other Carotinoids, and Prostate Cancer Risk: a Nested Case-Control Study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial", Cancer Epidemiol Biomarkers Prev, May 2007. The short conclusion: "...these results suggest that lycopene or tomato-based regimens will not be effective for prevention of prostate cancer." This finding was in contrast to the earlier boost for lycopene from the 2003 meta-analysis which found a 10% - 20% reduction in prostate cancer risk from a high tomato and lycopene intake, "weighted strongly by findings from the large Health Professionals Follow-up Study". The Health Professionals studies found high lycopene levels associated with less aggressive prostate cancer, and less prostate cancer in men 65 years or older and in men with a family history of prostate cancer. The hope for a protective benefit from lycopene, the most potent antioxidant carotenoid, 80% derived from tomato products, was that it would combat the free radical oxidative stress to the prostate that results from androgen exposure over time.

In the Hutchinson's prospective study 692 prostate cancer patients were compared with 844 matched controls and found that "No association was observed between serum lycopene and total prostate cancer [odds ratio, 1.14] for the highest versus the lowest quintile," and no association with aggressive prostate cancer. The eight-year study followed participants who "were selected from those who were assigned to annual standardized screening for prostate cancer." Conclusion: no support for lycopene in prostate cancer prevention.

So, Lycopene ... Is it a hold or a sell?

HORMONE INTERVENTION: Intermittent Androgen Deprivation: Very Likely An Idea Whose Time Has Come

Although the final judgment about the comparative effectiveness of IAD to continuous treatment awaits the completion of two ongoing major randomized trials, nonetheless there is substantial early support for IAD's equivalency of outcome with clear benefits for quality of life (QoL). In his review of IAD (BJU Int, Jan 2007) Dr. Tunn, Frankfurt, Germany, points out that "It can be used in any clinical situation where continuous AD (CAD) treatment could be applied." Additionally, "The potential advantages of IAD over CAD therapy are an improved QoL, a prolonged period of androgen independence, a reduced incidence of the side-effects normally associated with AD therapy, and a decrease in the cost of care." At the recent AUA meeting he presented data from a 244 man study that showed no significant difference in the 2-year rate of progression to androgen independence between CAD, 6%; and IAD, 8.3%. Both strategies showed a similar time to eventual PSA progression - about two years. At the meeting Dr. Gleave, UBC, indicated a desire for stronger data, which may in fact come partly from the contribution from his own Vancouver group's participation in the North American cooperative trial in which this issue is under study in 1300 men .

The Vancouver team published (Bruchovsky, CANCER, MARCH 1, 2007) useful data about the dynamics of IAD that will inform the usage of this management strategy: "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."

Their regimen: When the PSA rose to ≥4 ng/mL, a 4-week lead in with an anti-androgen was followed by Lupron for a total treatment time of 36 weeks. Therapy was then discontinued in those 103 men whose PSA dropped to below 4 ng/mL at both 24 and 36 weeks. Therapy was resumed when the PSA level reached ≥ 10 ng/mL. Cycle 1 was initiated in the 103 man cohort; and cycle 2 was initiated in 86 patients; cycle 3 in 56; cycle 4 in 26; and cycle 5 in 7 patients.

What was learned?

1) The mean value of PSA at the start of Cycles 1 through 4 ranged from 18.5 ng/ml to 11.9, but regardless of the PSA value the PSA fell by a average reduction of 95.2% in *every* cycle, and followed the characteristic bi-phasic pattern with the steep initial drop followed by the slow longer gradual decrease. The initial sharp drop they believe "represents an initial inhibition of PSA syntheses over the first 8 to 10 weeks, after which apoptotic cell loss accounts for the further [slower] reduction in serum PSA." This recurring pattern led to the suggestion that the 36 week treatment period could plausibly be lessened.
2) The duration of the time-off-treatment was inversely proportional to the PSA at the start of AD. The optimal example was seen in the group starting treatment with a PSA in the range of 4 - 10 ng/ml wherein the time-off-treatment was 90.7 weeks for Cycle 1; 66.5 weeks, Cycle 2; 26.2 weeks, Cycle 3; and 22.7 weeks, Cycle 4. Groups with higher baseline PSA values had shorter time-off periods. Correspondingly, the duration of time-off was related to AD induced nadir of PSA: in Cycle 1 for a PSA nadir of ≤ 0.2 ng/mL the duration of time-off was 75.7 weeks; for PSA nadir of 0.2 to 1, 53.5 weeks; for nadir 1 to 2, 37.2 weeks; and for a nadir of >2, 36.5 weeks.

The recovery of testosterone to low normal level was seen in 75% of men in cycle 1 within 5 months, but this percentage decreased in Cycles 2, 3, and 4 to 50%, 40%, and 30%, respectively. The recovery, however, was sufficient to restore hemoglobin to normal levels in successive cycles.

Bottom Line: It is likely that intermittent androgen deprivation will be found to be a validated alternative to continuous therapy. The details of the dynamics of IAD provided by the Vancouver group will usefully inform the application of this strategy.

SALVAGE TX FOR PRIMARY TX FAILURE: "Predicting The Outcome Of Salvage Radiation Therapy For Recurrent Prostate Cancer After Radical Prostatectomy, (JCO, May 2007)

This very useful and authoritative resource by Stephenson and 19 other well known prostate cancer experts (including Dr. Dan Lin, UW) is based on follow-up of 1540 patients from 17 North American tertiary referral centers. The article provides a nomogram giving 6-year progression free probabilities that integrate the weighted contribution of 11 standard clinical variables. The overall message is now well recognized: the *earliest* institution of salvage radiation therapy (SRT) after established PSA recurrence yields the best outcome. "Before SRT, all patients had a PSA level of 0.2 ng/mL or higher at least six weeks after RP followed by another higher value, or a single PSA of 0.5 ng/mL or higher."

Regarding the morbidity of SRT: "Mild to moderate acute rectal and genitourinary toxicity is seen in the majority of patients, but the reported incidence of acute grade 3 or 4 complications is less than 4%. Late grade 1 to 2 rectal and genitourinary toxicity are reported in 5% to 20% of patients, and late grade 3 toxicity is less than 4%."

An accompanying graph plots the proportion of men free of progression against the time in months from salvage radiotherapy according to four PSA ranges - 0.50 ng/mL or less; 0.51 to

1.0; 1.01 to 1.5, and more than 1.50. The proportion free of progression at 6 years associated with those ranges were: 48%; 40%; 28%; and 18% respectively. But the real value of their analysis lies in the nomogram which allows individualization of probable outcome by integrating a patient's values for the 11 parameters entered onto a continuous variable scale. The authors note that salvage XRT is conventionally recommended to patients estimated to be at low-risk for recurrence, but "Our study demonstrates that select patients with a short PSADT or Gleason grade 8 to 10 cancer may also benefit from SRT.

Dr. Kattan said that this nomogram will be soon be available on-line at "www.nomograms.org."

NEW AGENTS FOR TREATMENT: Early In Development: A Novel Gene Therapy For Prostate Cancer

We should wish success to Dr. Garen and his research team at Yale as they continue to pursue their daunting and pioneering project aimed at seducing cancer cells to provide the means for their own suicide. And although success in applying this therapy to humans may be far off, or even not achievable, it is intriguing just to know what they are attempting - a little glimpse into the sophistication of therapies to come.

Dr. Garen, a professor of molecular biophysics and biochemistry, initially presented his strategy in a 2001 article in the Proc Nat Acad Sci, "Targeting tissue factor on tumor vascular endothelium cells and tumor cells for immunotherapy in mouse models of prostate cancer."

The research is premised on the observation, made early on by Judah Folkman, that the neovasculature called forth by a developing tumor mass is significantly different from normal blood vessels, and as such displays a uniquely different array of endothelial antigens. The target antigen in this case is a transmembrane receptor, "tissue factor (TF)", also displayed on cancer cells. Dr. Garen has synthesized a novel gene that codes for an antibody-like immunoglobulin (he named it "Icon") that exhibits strong affinity for TF. When the Icon/TF complex is affixed to the endothelial surface a host cytolytic immune response kills the cells bearing the TF/Icon. Although direct IV administration of Icon carried by a viral vector was an option, Dr. Garen instead chose to encapsulate the synthetic gene in liposomal nanoparticles. This is a move to safety since other studies have been showing that the introduction of viral vectors can occasionally promote oncogenic transformation of the target cells. In information released by Yale, Dr. Garen was quoted: "The advantage of nanoparticles is that they do not reproduce, are not immunogenic, and are easier to produce than adenoviral vectors. The nanoparticles will have a tag [not the "Icon"] on their outside that binds to tumor blood vessels."

After IV administration the gene package is engulfed into the tumor cells which display the target antigen, TF, and is then incorporated into nuclear DNA, instructing the cells themselves to make the Icon molecules. Once the Icon antibody is synthesized by the tumor cells, and after entering the circulation, the Icon molecules home to TF antigens on metastatic tumor cells and their vascular endothelium causing cell destruction. Early work found no harm to non-TF bearing cells.

Earlier tests that employed an adenoviral delivery vector resulted in long-term regression of transplants of human prostate cancer into mice. Continuing work by Dr. Garen's team, supported by the Competitive Awards Program (2006) of the Prostate Foundation, will attempt to extend these observations now using liposomal nanoparticles to deliver the synthetic gene to animal models implanted with human metastatic prostate cancer. Let's hope Icon is a success.

[I appreciate Dr. Alexander Steven's bringing this material to my attention.]