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PERMANENT SEED BRACHYTHERAPY FOR HIGH-RISK PROSTATE CANCER: *A Comprehensive Treatment Concept and Skillful Execution = Excellent Results*

The hallmark of "high-risk" prostate cancer is a preponderance of advanced localized disease, i.e. high rates of extracapsular extension, seminal vesicle involvement, perineural invasion, and high percentage of positive biopsy cores. Successful treatment must be based on a regimen that takes this biology into account. Drs. Greg Merrick, Kent Wallner and colleagues report excellent results from their comprehensive approach in "Prostate cancer death is unlikely in high-risk patients following quality permanent interstitial brachytherapy, *BJU International,* 2010. The actuarial prostate cancer specific survival (CSS) at 12 years was 94.2% (mortality: 5.8% of 284 patients). Death *unrelated* to cancer was 2.3 times the cancer specific death rate. This excess was comprised of cardiac related deaths, 14%; non-prostate cancer deaths, 8%; and other, 8%. The authors were sufficiently impressed with the rate of cardiovascular deaths so that their total approach includes an extensive life-style modification program.

The therapy regimen employed Palladium-103 (91.5%), supplemental external beam radiotherapy (90.5%), and 63.0% of men received androgen deprivation therapy (≤6 months, 18%; >6 months, 45%). "*At implantation, the prostate gland, periprostatic region and the base of the seminal vesicles* [proximal 1.0 cm] *were implanted"* [emphasis mine].

RESULTS: "Twelve-year CSS, biochemical progression-free survival, and OS were 94.2%, 89.0%, and 69.7%." The bPFS was based on a threshold of PSA ≤0.40 ng/ml. Median age was 68 years, and median follow up 7.8 years. "When OS was stratified by patients with 0-3 vs ≥4 comorbidities, the 12 year OS was 73% and 52.7% (p=0.036). "Androgen deprivation significantly improved biochemical control rates." bPFS was 93.4% for the 18% of men receiving ADT for longer than 6 months; 91.8%, 45% for ADT less than 6 months; and 82.6% for hormone-naive men. ADT was especially useful for men with pre-treatment Gleason scores of 7 and PSA levels >20 ng/ml.

High-risk patients with less than 34% of biopsies positive for malignancy had a 96.0% 12-year bPFS while for those with greater involvement the bPFS was ~86%.

Caveat: "It has also become increasingly evident that biochemical control following brachytherapy is highly dependent on implant quality." The concern for the high rate of cardiac deaths "led to the implementation of physical rehabilitation programs (including dietary modification, smoking cessation, aerobic and resistance training, and aggressive management of hypertension, diabetes and hyperlipidemia as well as age-appropriate screening) to promote healthy lifestyles."

BOTTOM LINE: An expertly conducted and well-conceived, biologically based treatment regimen for men with high-risk prostate cancer can yield excellent results.

CABOZANTINIB: Startling Responses Reported at June ASCO Meeting in Metastatic Castrate Resistant Prostate Cancer

An interim report (Abstract 4516) of a Phase II study conducted by a consortium of cancer centers cited the remarkable complete and partial response rate of 86% (56/65) in bone lesions after 12 weeks of treatment. Stable disease occurred in 12% and 2% showed progression.

The response of soft tissue lesions was equally impressive - shrinkage of nodal disease, 87%; visceral disease decrease, 37%. At 12 weeks disease control was seen in 71% and 87% were less likely to experience progression than men in the placebo group. "Improvement in pain from baseline was seen in 56 patients (67%), and 31 patients (56%) decreased or discontinued narcotics for pain."

The agent responsible for these stunning results is the newly developed multi-tyrosine kinase inhibitor, cabozantinib (XL184), formulated by Exelixis, Inc. The dose in the study was 100 mg daily *orally*. By blocking kinase activity, the drug inhibits the expression of the cancer related genes, MET and VEGFR (and possibly others). MET (Hepatic Growth Factor 1) is upregulated in metastatic prostate cells in states of androgen deprivation. "MET is implicated in tumor invasion and metastases, and the synergistic effects of MET and VEGFR promote tumor angiogenesis." Cabozantinib effects its inhibiting function not only in the cancer cell, but also in the microenvironment, which is currently understood as an essential partner in cancer growth. Biomarkers related to bone osteoblasts and osteoclasts (total alkaline phosphatase and C-Telopeptide) showed a favorable decrease in the majority of men, consistent with the bone responses.

Moderate side effects were observed: Grade 3 fatigue, burning feet ("hand-foot syndrome"), and hypertension - 16%, 6%,and 6% respectively.

Although it is early in the evaluation of this drug, the initial results are extremely promising. Additional Phase II trials are in progress.

INTERMITTENT ANDROGEN SUPPRESSION for PROSTATE CANCER:

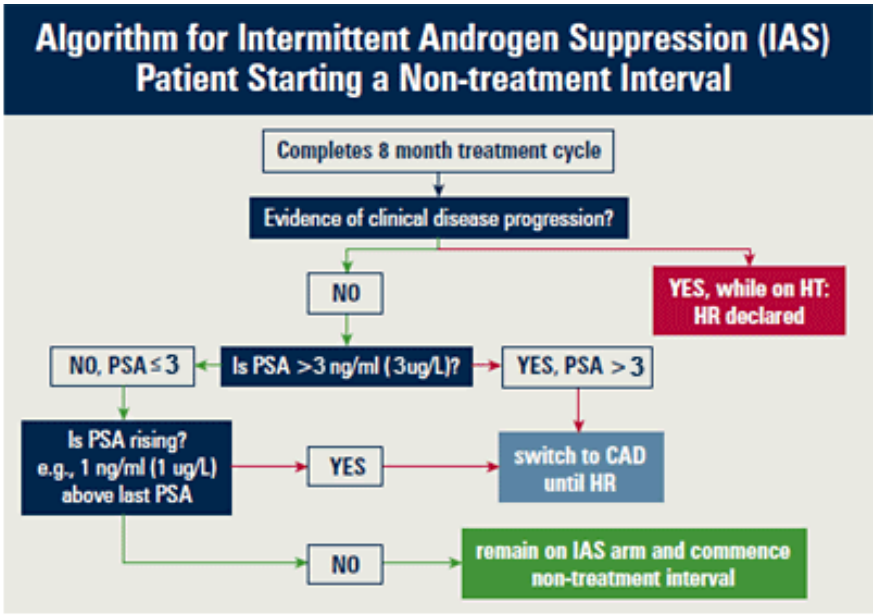
Abstract 4514, ASCO June 2011 Meeting

A study was conducted by the National Cancer Institute of Canada comparing a regimen of intermittent androgen suppression (IAS) in 690 men with continuous androgen deprivation (CAD) in 696 men. The conclusion: "IAS is non inferior to CAD with respect to survival," - a statistically apt way of stating equivalence.

Eligibility required a rising PSA value to >3 ng/ml after primary treatment and no evidence of metastatic disease on scans. Before treatment initiation an interval of greater than 12 months was required following surgery, surgery/salvage radiation, radiation, or radiation/hormone therapy. The intermittent regimen involved 8 month treatment cycles followed by a rest period. Therapy was restarted when the PSA rose above 3 ng/ml. Median patient age was 74.2 years; follow up, 6.9 years; number of cycles, 1 - 9 with a median of 2. The primary endpoint was overall survival.

Note in the schema below that after 8 months of IAS if a man's PSA does not drop below 3 ng/ml he is switched to CAD. And after a treatment cycle even if the PSA falls to less than 3 ng/ml, a rising PSA during the treatment cycle of 1 ng greater than the last value also prompts a switch to CAD.

The full schema: (HR = Hormone Resistance)



Source: *ASCO Daily News*, **June 7, 2011**

BOTTOM LINE: On the basis of the results of this large randomized Phase III trial, "ASCO 2011 endorsed the concept that IAS now be presented to patients at the time of 'biochemical PSA recurrence' in the absence of metastatic disease," *Advances*, Prostate Cancer Foundation, July 2011. (More details will likely be presented when the study is published.)

RESULTS:

1) Quality of life analysis: "IAS patients had better QoL in physical function ($p<0.01$), fatigue ($p<0.01$), urinary problems ($p=0.01$), hot flashes ($p<0.01$), desire for sexual activity ($p<0.01$) and erectile function ($p<0.01$) "35% of IAS had full testosterone recovery."

2) Time to hormone resistance was statistically significantly improved on the IAS arm. ($p=0.024$).

3) No difference was recorded between study arms in regards to cardiac events and osteoporotic fractures.

4) Median overall survival for IAS was 8.8 yrs; for CAD, 9.1 yrs. Disease specific death occurred in 18% of men on IAS compared to 15% on CAD.

5) The cost of IAS was 27% of the cost of continuous treatment (Ref. Prostate Cancer Foundation).

ACTIVE SURVEILLANCE AND 5ALPHA-REDUCTASE INHIBITORS

A group of investigators from the Princess Margaret Hospital in Toronto have reported "The 5ARIs were associated with a significant lower rate of pathologic progression and abandonment of active surveillance [AS]" (Finelli A, *European Urology. Apr 2011).*

A total of 288 were studied. "Pathologic progression was evaluated and defined as Gleason score >6, maximum core involvement >50%, or more than three cores positive." Patients were randomized to receive a 5ARI or none. At a medium follow-up of 38.5 months, a retrospective analysis compared those men taking a 5ARI to those who were not. The pathologic progression rate was 18.6% for those on 5ARIs versus 36.7% for no treatment (p=0.004), and the men in the ARI group were less likely to abandon AS, 20% v. 37.6%.

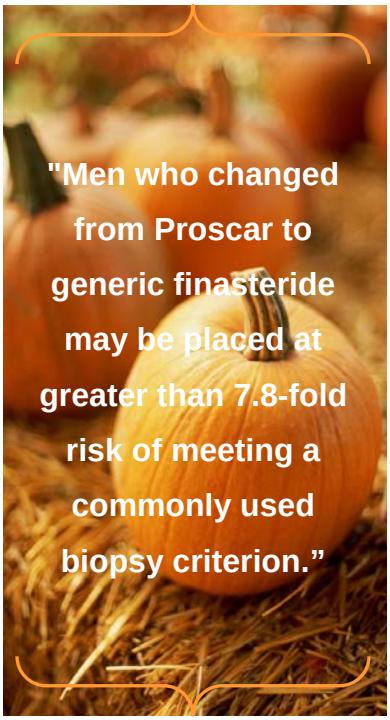
SWITCHING BETWEEN 5ALPHA-REDUCTASE INHIBITORS

Switching between 5ARIs can alter PSA velocity. The reasons for changing can relate to insurance coverage or cost; or impression of drug superiority or interchangeability. A switch from a branded drug to its generic formulation is often considered safe because of a belief of bioequivalency in terms of safety and efficacy. However, as pointed out by Helfand, "Consequences of Switching 5alpha-Reductase Inhibitors on Prostate Specific Antigen Velocity" (*J Urol July 2010),* "branded and generic formulations must contain the same active medications, but inactive ingredients, including preservatives, binders, etc., may be substituted."

The study analyzed changes in PSA and PSAV values in men whose PSA records were suitable for calculation of PSAV. Eight men changed from Avodart (dutasteride) to generic finasteride (group 1); 21 switched from Avodart to Proscar (group 2); 49 changed from Proscar to Avodart (group 3); and 77 changed from Proscar to generic finasteride.

The mean PSAV *increased* in both group 1 and 2 after switching from Avodart to either Proscar or its generic (p=0.05). In the men switching from Proscar to Avodart the rate of improvement in PSAV was slightly better on Avodart. However, in group 4, "More than 40% of men experienced increased PSAV when switched from Proscar to generic finasteride.

The authors assessed the clinical consequences of their findings in terms of a decision to perform a prostate biopsy based on PSAV values. The authors concluded: "Men who changed from Proscar to generic finasteride may be placed at greater than 7.8-fold risk of meeting a commonly used biopsy criterion. Using the same cutoff of a PSAV of 0.35 ng/ml per year, we found that switching to a dual 5ARI [Avodart] was associated with a decreased risk of unnecessary biopsy."



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BRACHYTHERAPY VERSUS EXTERNAL BEAM RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER:

A Head to Head Comparison

A well-balanced and statistically credible retrospective analysis of this comparison was presented by Zelefsky and colleagues (Department of Radiation Oncology, Medical Physics, and Epidemiology Biostatistics, Memorial Sloan - Kettering Cancer Center): "Comparison of Tumor Control and Toxicity Outcomes of High-dose Intensity-modulated Radiotherapy and Brachytherapy for Patients With Favorable Risk Prostate Cancer", *Urology. 2011 Apr.*

The authors' conclusion: "Patients should be counseled that, with well-delivered brachytherapy [BT], the biochemical control rates can be 5%-10% better than can be achieved with high-dose IMRT." *The difference appears to result from the significantly higher dose that brachytherapy can safely deliver to the prostate gland.*

This study spanned from 1993 to 2003 and involved 281 men treated with IMRT compared to 448 men receiving Iodine-125 brachytherapy. Low-risk localized disease was defined as Stage T1-T2a, Gleason score ≤6, and pretreatment PSA level of <10 ng/ml. PSA relapse was based on the "nadir plus 2 ng/ml" definition; median follow-up time was 77 months.

DOSE MATTERS: For IMRT greater than 90% of men received in excess of 95% of the prescription dose of 81 Gy to the planned treatment volume, and this volume never received more than 111% of the prescription dose.

For brachytherapy the prescribed dose was 144 Gy. "The median volume of the prostate receiving 100% for the prescription dose was 96%, and the median dose to 90% of the prostate was 170 Gy. Significant portions of the gland received doses in excess of 250 Gy.

These clinicians employ "real-time intraoperative planning which [in their opinion] has demonstrated more consistent delivery of the radiation dose with fewer associated morbidities." They point out that "the presence of baseline significant urinary obstructive symptoms, larger prostate size or other comorbidities" might favor the choice of IMRT.

The author's state: "We believe that these improved biochemical control outcomes were related to the greater biologic doses that could be delivered to the tumor with brachytherapy compared to ERBT [external beam radiotherapy]." Other studies have shown that IMRT doses in excess of 81 Gy are associated with increasing side effects.

RESULTS: "The 7-year prostate-specific antigen relapse-free survival rate for the brachytherapy and IMRT groups was 95% and 89% (p=0.004)" Freedom from distant metastases was excellent in both groups at 7 years: 100% freedom for BT, 99.2% (2 patients with metastases) for IMRT.

TREATMENT TOXICITY: Late significant urinary toxicity (Grade 3) was infrequent: 2.2% BT v. 1.4% IMRT. Less serious urinary side effects (modest frequency and dysuria which improved over time) were seen in 15.6% of men for BT v. 4.3% for IMRT. Late rectal complications (usually rectal bleeding - Grade 2) occurred from BT in 5.1% v. 1.4% for IMRT. There was no significant difference for more severe rectal complications: 1.1% for BT v. 0% IMRT (P=0.19).

When potency was defined as "the ability to achieve an erection sufficient for sexual intercourse", among those men who were potent prior to therapy, 35% (BT) and 44% (IMRT) developed post-treatment impotence (p=.04). The average age for men in this comparison was 65 years for BT and 66 for IMRT.

The authors acknowledge "the abundance of variables affecting potency" and therefore they "caution patients not to select their therapy according to presumed advantages of one therapy over another for a lower incidence of sexual dysfunction."

BOTTOM LINE: Zelefsky's study supports their conclusion that "the 7-year biochemical tumor control was superior for intraoperatively planned brachytherapy compared with high-dose intensity-modulated RT."..."From our present results, our treatment preference for patients with low-risk prostate cancer has been to favor brachytherapy because of the improved tumor control outcomes."